

**HORMONAL and NEUROGENIC
CARDIOVASCULAR DISORDERS**

Hormonal and Neurogenic Cardiovascular Disorders

ENDOCRINE AND NEURO-ENDOCRINE FACTORS
IN PATHOGENESIS AND TREATMENT

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Macbeth to Doctor:—

"Cleanse the stuffed bosom
Of that perilous stuff
Which weighs upon the heart."

(Act V, scene 3)

*To the memory of four pioneers who possessed both the vision
to find facts and the courage to draw conclusions:*

· ARTHUR BIEDL, Endocrinologist

WALTER B. CANNON, Physiologist

HARVEY CUSHING, Neurosurgeon

KAREL F. WENCKEBACH, Cardiologist

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Preface

The breath-taking rapidity with which knowledge of endocrine functions and interrelations has expanded during recent years entails unexpected demands on the receptiveness and flexibility of thought not only of the endocrinologist but even more so on the part of the representatives of many other medical domains into which endocrinological pathogenic considerations and therapeutic procedures have made extensive and revolutionary inroads. A widespread reaction of surprise and incredulity is a necessary and unforeseeable

idea must traverse, no matter how dimly and grudgingly, the growing importance of thinking in terms of hormonal biochemical effects, even in fields which for decades had seemed far from any endocrine implications.

The swinging and swaying of interests and attitudes among supposedly detached investigators in the realm of supposedly objective science are in themselves a fascinating psychological spectacle, not unlike the tides of political ideologies. Newly discovered facts have little or no prospect of being widely accepted, unless they are endowed with what one might call "brain appeal", a fortuitous congeniality with existing conscious or subconscious trends of thought, a catchy technical designation or the backing of a glamorous authority. On the other hand, well established knowledge is sometimes relegated into oblivion under the detracting spell of differently focused conceptions of a more recent vintage.

With full awareness of these shortcomings which beset the searching human mind, I have for some time been concerned about the unnatural gap which separates the dramatically developing field of endocrinology and of its neuroendocrine aspects from the not less fruitful but more conservative advances of clinical cardiology. The outstanding triumphs of the latter were attained in the spheres of cardiac surgery, electrocardiography, hemodynamics. These triumphs have created a series of intense and important problems and a

concomitant which almost entirely disregards the profound interferences of neurohormones and hormones in myocardial metabolism and function. Each of the two specialties has created such a vast and forbiddingly intricate ideological and technical scientific armamentarium of its own that only relatively few disciples of either one feel the impulse to venture whole-heartedly across the dividing line.

To my knowledge, no general survey of the

their illustrations. To the publishers, The Williams & Wilkins Company, I am indebted for generous cooperation and valuable advice.

I expect to be criticized not only for the inevitable errors and omissions which are bound to slip into an extensive one-man job like this, but even more so for a certain degree of dogmatism in the presentation of my personal views which pervade the entire opus. Numerous bone-dry factual observations have been unearthed from the cemeteries of the international literature. In attempting to vitalize them and to incorporate them into a system of clinical reasoning, I have sometimes deliberately infringed upon the code of cautious understatement. This, however, is a factor inherent in the dynamics of crusading for any idea and may be excused on these grounds.

It is the purpose of this book to convince cardiologists and other physicians that neuroendocrine and endocrine influences play a fundamental and decisive part in the origin and therapeutic amenability of many cardiovascular disorders and that it is necessary to incorporate the established results and concepts of contemporary neuroendocrinology and endocrinology into everyday clinical thinking and acting. I feel strongly that the future

grow in

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or wan

detail. ~~which is~~ ^{which is} ~~presented~~ ^{presented} in this review to the multitude of problems under discussion, for as we all know, "Research is the systematic penetration toward new levels of ignorance."

Burlington, Vermont

W. RAAB

tional and structural derangements of the cardiovascular system, has yet appeared in the literature. However, the desirability of such a review had been pointed out in some quarters for many years. At the present time, the number and conclusiveness of pertinent individual observations have ripened to a stage which appears favorable for a broad representation of the principles involved in the many entanglements of endocrinology, neurovegetative physiology and clinical cardioangiology. Brickstones, beams, and arches for a solid edifice of mutual integration are ready in large quantities. They have been produced by thousands of investigators throughout the world with awe-inspiring ingenuity and assiduousness. While most of the groundwork had been laid in European scientific and clinical institutions, the gravitation center of modern developments has decidedly shifted to the western hemisphere as illustrated by the fact that not less than 60 per cent of the literature on which this study is based has originated in the United States. It seems about time to outline an architectural plan according to which these vast masses of available building material can be assembled for their ultimate destination.

I would not have dared to undertake such a formidable task, nor probably even have been particularly interested in the subject, were it not for the coincidence that my earlier training in both clinical and experimental work happened to take place under the inspiring guidance of two pre-eminent leaders in the fields of endocrinology and cardiology respectively: Arthur Biedl in Prague and Karel F. Wenckebach in Vienna. Later, during a Rockefeller fellowship at Harvard, the stimulating personal contact with two towering figures of American medicine, Walter B. Cannon and Harvey Cushing, left indelible imprints on my mind and, being a clinician with investigative leanings, I have continued to this day in the serenity of the Green Mountains to pursue my hobby of acting as a sort of interloper between two alienated camps of medical investigation at the risk of being regarded with some suspicion by both.

I wish to express my gratitude to those public and private agencies which financed much of my clinical and experimental work through the appropriation of research grants: the U. S. Public Health Service, National Heart Institute, the Rockefeller Foundation, the John and Mary B. Markle Foundation and the American Medical Association; to the U. S. Department of State for the facilitation of a very profitable study period in post-war European universities, and to those co-workers and colleagues on both

for able and resourceful technical assistance, to Mrs. Jean Healy for her untiring and efficient secretarial help in the preparation of the manuscript, and to those authors who gave me the permission to reproduce some of

How To Use This Book

Since it is the purpose of this book to point out the interrelations and the overlapping of two separate fields of Medicine, namely of Endocrinology and Cardio-Angiology, the subject matter was arranged in three main sections in the following manner:

I Experimental cardiovascular effects of hormones and neurohormones

II. Cardiovascular features in endocrine and neuroendocrine syndromes.

III. Endocrine and neuroendocrine factors in cardiovascular syndromes.

Section II may be of greater interest to the clinical endocrinologist; Section III, to the cardiologist, internist and practicing physician. Section I is intended to serve all readers as a source of condensed information concerning the experimentally established fundamentals of neurohormonal and hormonal interference in cardiovascular metabolism, function and structure.

Those who wish to acquaint themselves first with the general principles upon which the clinical discussions are based are urged to notice that —

..... 224 26 discuss a number of points which, although widely unknown or disregarded among clinicians, constitute the backbone of the subsequent deliberations and practical applications concerning the origin and treatment of some of the most common forms of cardiovascular disease

Cross-references from section to section, dispersed throughout the text, and synoptic surveys at the end of each of the three main sections (pp 60, 230, 515) will help to keep the manifold interrelations of endocrine, neuroendocrine and cardiovascular features in mind.

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II

EXPERIMENTAL CARDIOVASCULAR EFFECTS OF HORMONES AND NEUROHORMONES

Adreno-Sympathogenic Catecholamines (Epinephrine and Nor-Epinephrine)

The adreno-sympathogenic catecholamines are believed to be derivatives of hydroxytyramine, which, in turn, is a product of decarboxylation of the amino acid dihydroxyphenylalanine¹³⁴⁹. Both of these latter substances exert only weak effects on the cardiovascular system^{367, 2197}. Epinephrine forms the bulk of adrenal medullary secretion which is governed by the hypothalamus^{1342, 1442}, by certain central mechanisms in the spinal cord^{1344, 1349}, by the sympathetic system via the splanchnic nerves¹¹⁰ and apparently also by the blood level of the sympathomimetic catecholamines themselves¹³⁶². The liberation of adrenal medullary hormonal material into the blood stream and its utilization in the tissues occur under a variety of stressful situations, such as muscular exercise, emotional tension, pain, sexual intercourse, cold, heat, hemorrhage, intoxications, etc.,^{110, 423, 1352} and under the influence of a reflex mechanism which originates in the carotid sinus³⁷⁵. Epinephrine seems to be elaborated also in some other parts of the body, e.g., in groups of chromaffine cells inside the sympathetic ganglia⁴²⁹ and inside the heart muscle¹⁴⁴¹. Fluorometric investigations^{1359, 1942} suggest that epinephrine is discharged by the adrenal medulla and by the chromaffine elements of the sympathetic system in relatively large quantities in a non-dialysable protein-bound form⁴³ ("adrenalinogen"). This compound is biologically inactive but supposedly serves to replenish the stores of the peripheral sympathetic neurosecretory structures when they are depleted by having liberated their catecholamine supplies into the respective effector cells in a biologically active form. Sympathetic stimulation was claimed to make the transformation from the inactive into the active state possible and to start simultaneously the mechanism of reparatory discharges of "adrenalinogen" into the circulation. The findings concerning "adrenalinogen" have not yet been confirmed however.

Nor-epinephrine (arterenol), a non-methylated homologue of epinephrine, is now considered identical with "sympathin"^{114, 906, 1092, 1351}. It is probably the immediate precursor of epinephrine^{291, 428, 422, 1354, 1356, 1363} and constitutes up to 30 per cent of the hormone content of the adrenal medulla^{110, 1129, 1354, 1364} and of its secretion¹⁴⁹². The factors which promote its secre-

rine is present in abundant quantities in the entire sympathetic system whose postganglionic nerve endings discharge it together with small amounts of epinephrine³⁰³ as their specific chemical neurosecretory mediator into the respective innervated cardiovascular effector cells³⁰⁷ under the influence of sympathetic excitation^{207, 2702}. Recent findings^{1659a} indicate that central nervous stimulation provokes the passing of nor-epinephrine from the arterial walls into the blood circulation.

Some sympathetic nerves, especially those supplying the skeletal musculature^{122, 552, 1012}, contain vasodilator fibers. They act under hypothalamic control³⁸². The nature of their chemical transmitters is still controversial. Both adrenergic³⁸² (epinephrine ?) and cholinergic¹⁰¹² (acetylcholine ?) activity are being suspected.

According to some investigators^{17a, 1905a}, the excitatory and inhibitory pharmacodynamic effects of the sympathomimetic amines are largely determined by the nature, number and sensitivity of specific "receptors" in the responding tissues. The heart muscle in particular is believed to contain only excitatory^{17a} or undifferentiated^{1905a} but not any inhibitory receptors for the sympathomimetic catecholamines.

Acetylcholine, the physiologic stimulant of adrenergic neurosecretion^{213, 637, 963, 1341}, liberates epinephrine-like sympathomimetic material in the myocardium¹³⁴¹. It has been claimed that "sympathin", in turn, liberates acetylcholine in the cardiovascular cells^{632, 642}. This interesting hypothesis of a subtle interplay of both antagonistic neurohormones requires further investigation.

The heart muscle possesses an outstanding tendency to absorb and to accumulate circulating epinephrine (Fig. 1),* which markedly exceeds that

* Since a considerable portion of the writer's personal observations and con-

It reveals the presence of material which fulfills the three requirements: (1) Production of a blue color with arsenomolybdic acid, (2) Non adsorbability by $Al(OH)_3$ at pH 4.0, (3) Quantitative adsorbability by $Al(OH)_3$ at pH 8.5. The latter conditions, by eliminating other chromogenic substances, restrict the specificity of the method to chromogens which carry at least two free hydroxyl groups in orthoposition. In biological substrates, this limits the specificity practically to the catecholamines, dihydroxyphenylalanine (DOPA), hydroxytyramine, nor-epinephrine, and epinephrine (by far the strongest color reaction being produced by the latter), and to ascorbic acid, the chromogenicity of which is so weak, however, that it does not seriously affect the readings as a rule. Thus, while the method cannot be claimed to be strictly specific for epinephrine and nor-epinephrine, its results are essentially determined by the quantity of these sympathomimetic catecholamines. It permits a fairly accurate and relatively convenient over-all evaluation of quantitative alterations of the adrenosympathogenic neurohormones, in-

of other tissues²⁶¹² (Fig. 2). This could be demonstrated both after injection of epinephrine and under experimental conditions which are known to be accompanied by epinephrine discharges into the blood: muscular exercise, exposure to cold, splanchnic stimulation, administration of acetylcholine (Fig. 1) and of large doses of insulin²⁶¹². Vitamin B₁ deficiency is another condition which favors an abnormal accumulation of epinephrine and nor-epinephrine in the heart^{1298a, 2720}. Administration of dihydroxyphenylalanine leads to the appearance of increased amounts of nor-epinephrine in the myocardium²¹¹⁴. On the other hand, sympathectomy with and without adrenal inactivation was found to be followed by a marked diminution of the sympathomimetic amines in the heart muscle^{111, 46, 1298a, 2711} (Fig. 1). A large part of the sympathomimetic substances present in the normal myocardium could be identified as nor-epinephrine pharmacodynamically and by means of paper chromatography²⁷¹⁰ (Fig. 3, 4). It constitutes 75 to 90 per cent of the cardiac sympathomimetic amines while the rest is epinephrine^{1206, 1301, 2608} and hydroxytyramine^{1298b}. Similar material was also extracted from the walls of large arteries¹⁰¹⁷ and veins¹⁰¹⁷ (Fig. 5). The human coronary vessels contain mostly epinephrine¹¹¹⁴. It is probable that the contractile cells of the smaller arterioles, which are innervated by sympathetic fibers, contain also active catecholamines⁴⁴⁸. Both epinephrine and nor-epinephrine are excreted with the urine, partly in active form, partly in an

cluding nor epinephrine, the
 is becoming increasingly appa
 tween the results obtained by
 sympathomimetic catecholamine and those obtained by the writer colorimetrically
 Furthermore, various experimentally produced quantitative alterations of the
 catecholamine concentration in tissues, as observed by the writer with colorimetry,
 were confirmed by others, using pharmacological methods.

TISSUE	BIOASSAY (GAMMA PER GRAM)	AUTHORS	COLORIMETRIC ASSAY (GAMMA PER GRAM)†	AUTHOR
Heart muscle (cat)	0.5-0.8	Cannon & Lissak ¹⁰⁸	0.9-1.8	Raab
Spleen	2-10	Euler ¹⁰¹	1-5	Raab
Adrenal glands	150-1320	Shan ²⁰²⁹	115-502	Raab
Sympathetic neurones	1-4.5	Lissak ²⁶⁵⁵	2.1-4.7	Raab
Vagus (cervical)	0-1	Lissak ²⁶⁵⁵	0.06-0.2	Raab
Sciatic nerve	0.6-1	Lissak ²⁶⁵⁵	0.09-0.4	Raab
Phrenic nerve	0	Lissak ²⁶⁵⁵	0	Raab

† Colorimetrically determined epinephrine equivalents (1 color unit equalling 0.001 gamma of epinephrine)

rine is present in abundant quantities in the entire sympathetic system whose postganglionic nerve endings discharge it together with small amounts of epinephrine³⁰⁵ as their specific chemical neurosecretory mediator into the respective innervated cardiovascular effector cells³⁰⁷ under the influence of sympathetic excitation^{297, 2702}. Recent findings^{1859a} indicate that central nervous stimulation provokes the passing of nor-epinephrine from the arterial walls into the blood circulation.

Some sympathetic nerves, especially those supplying the skeletal musculature^{132, 532, 1012}, contain vasodilator fibers. They act under hypothalamic control⁴³². The nature of their chemical transmitters is still controversial. Both adrenergic⁴¹² (epinephrine ?) and cholinergic¹⁰¹² (acetylcholine ?) activity are being suspected.

According to some investigators^{17a, 1903a}, the excitatory and inhibitory pharmacodynamic effects of the sympathomimetic amines are largely determined by the nature, number and sensitivity of specific "receptors" in the responding tissues. The heart muscle in particular is believed to contain only excitatory^{17a} or undifferentiated^{1903a} but not any inhibitory receptors for the sympathomimetic catecholamines.

Acetylcholine, the physiologic stimulant of adrenergic neurosecretion^{213, 457, 981, 1341}, liberates epinephrine-like sympathomimetic material in the myocardium¹³⁴¹. It has been claimed that "sympathin", in turn, liberates acetylcholine in the cardiovascular cells^{452, 463}. This interesting hypothesis of a subtle interplay of both antagonistic neurohormones requires further investigation.

The heart muscle possesses an outstanding tendency to absorb and to accumulate circulating epinephrine (Fig. 1),* which markedly exceeds that

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epinephrine and nor-epinephrine were found to diminish renal blood flow and to interfere with glomerular function^{221a}.

A marked increase of the vasoconstrictor efficiency of epinephrine in certain vascular areas is elicited by "VEM", a chemically undefined substance which was extracted from ischemic kidneys^{212, 219}, and by various tissue protein fractions, hypertensin and tyrosine²¹¹. The intensification of

% -50 ± 0 +50 +100 +150

HEART

KIDNEY

MUSCLE

LIVER

BRAIN

SPLEEN

FIG. 2 Average deviations (per cent) of tissue catecholamine concentration after injection of epinephrine, indicating the particular avidity with which the heart muscle absorbs circulating epinephrine (After W Raab, *Exp Med. & Surg* 1: 188, 1943)

the pressor effects of both epinephrine and nor-epinephrine through desoxycorticosterone²²⁴ and their weakening through sodium withdrawal²²⁰⁷ will be discussed later. Acting upon the brain, which is connected with the body only by nervous pathways, epinephrine produces a marked reduction of the blood pressure²²²⁷, apparently through interference of specific cerebral chemoreceptors. Cerebral vascular resistance is markedly increased by norepinephrine but not significantly altered by epinephrine^{1763a}.

The recently discovered phenomenon of blood "sludging" in small vessels under the influence of sympathomimetic amines¹⁸²³ may be of considerable

inactivated conjugated form^{282, 911, 936, 1560, 1950, 2799}, in increased amounts after physical exercise⁹¹² and during infusion of nor-epinephrine⁹¹⁴.

Functional Effects

HEMODYNAMIC EFFECTS. Both epinephrine and nor-epinephrine are highly efficient pressor substances, but the mechanisms of their respective pressor effects differ fundamentally. Epinephrine, which can be charac-

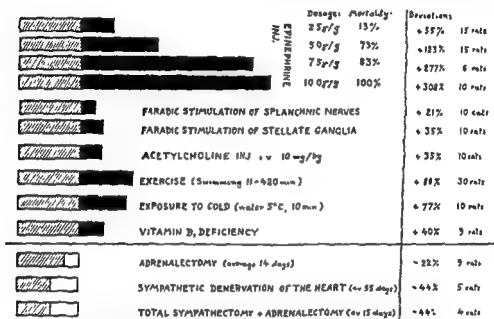


FIG 1 Average increase (black areas) and decrease (white areas) respectively of the catecholamine concentration in the heart muscle of animals under various experimental conditions. The average normal concentrations are indicated by the framed areas which appear wholly shaded in the 10 first bars and partially shaded in the last three bars (After W Raab, *Ann Int. Med* 28 1010, 1918) (For information regarding the method of assay, see footnote, pages 4, 5)

terized as a generally vasodilator agent^{1180, 2574}, especially in working muscles²⁷⁶⁷, exerts its pressor action largely through cardiac stimulation, resulting in an increased cardiac output^{1160 1251}. Accordingly, the diastolic pressure is much less elevated by epinephrine than the systolic pressure. Indeed, it frequently falls below the original level^{906 1518 1845 2704}. Only large doses of epinephrine (more than 0.3 gamma/kg/min.) were found capable of elevating also the diastolic pressure through general vasoconstriction¹⁷⁷. Nor-epinephrine, on the other hand, acts as an over-all vasoconstrictor and regularly raises both the systolic and the diastolic pressure^{439 177 1150 1554 1818, 2704, 3327}. The mean arterial pressure is augmented by nor-epinephrine more intensely than by an equal dose of epinephrine^{906 2351}. In dogs, both

hemodynamic and metabolic significance, but has not yet been thoroughly investigated.

Under the influence of "adrenolytic" drugs, such as the benzothioxane compounds, dibenamine, ergot alkaloids, prisco-line and others¹⁵¹, the pressor effect of epinephrine is usually converted into a fall of blood pressure. That of nor-epinephrine is only weakened by the same agents^{152, 153}.

CARDIAC EFFECTS. Injected or secreted epinephrine does or does not elicit cardiac acceleration, depending upon the degree of reflexory vagal interference¹⁵⁴. The effect of injected nor-epinephrine on the heart consists regularly of a distinct retardation^{155, 157, 158, 159, 160, 161, 162}. This is to be explained as the result of a concomitant stimulation of the vagus, due to the influence of the elevated mean pressure upon the carotid sinus^{159, 160}, which is said to be also directly sensitized by nor-epinephrine¹⁶³, and possibly to the Bezold-Jarisch reflex, which originates in the ventricular and auricular walls^{164, 165, 166, 167, 168}. After inactivation of the vagus through section or atropine, both epinephrine and nor-epinephrine act as pure cardio-accelerators^{157, 169, 170, 171, 172, 173}.

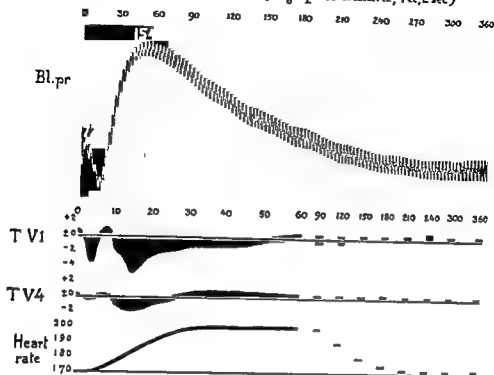
It is important to keep in mind that the cardiac effects of injected or infused and circulating nor-epinephrine do not represent the physiological action of nor-epinephrine which reaches the heart muscle by its natural pathways, the postganglionic sympathetic fibers, and which does not elicit antagonistic vagal reflexes via the peripheral pressoreceptors. This fact is usually overlooked in the application of results, obtained with nor-epinephrine injections, to the interpretation of its physiological properties. Concluding from the effects of experimental stimulation of the cardiac symp-

... of nor-epinephrine a purely sympathomimetic direct action upon the heart, practically identical with that of epinephrine (Fig. 6)

Large doses of epinephrine are apt to provoke arrhythmias, such as atrio-ventricular rhythm, extrasystoles, auricular fibrillation and fatal ventricular fibrillation^{160, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185}. Tachycardia and extrasys-

FIG. 3 Qualitative and quantitative ...

HEART SYMPATHIN (COW, 15 γ -equ. colorimetric, 4 cc, 2 sec)



ARTERENOL (15 γ , 4 cc, 2 sec)

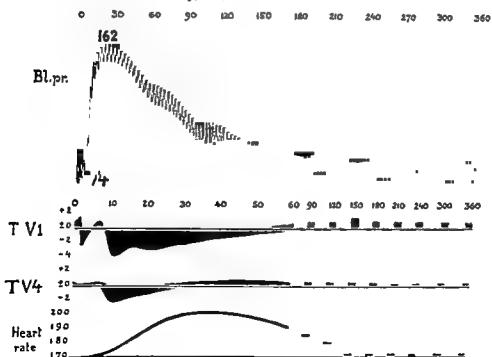
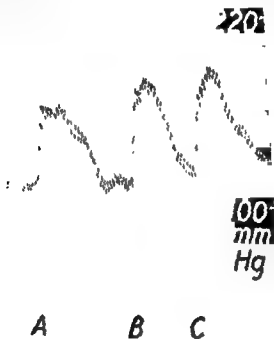


FIG 3

tions and subjective discomfort connected with the artificial administration of nor-epinephrine as compared with that elicited by epinephrine^{41, 42}. Directly discharged neurogenic nor-epinephrine increases the cardiac stroke volume and the heart rate, thus augmenting cardiac output.

A greater, potentially pathogenic, importance than that of the aforementioned dynamic cardiac effects of the sympathomimetic catecholamines



(Suppl 56) 1, 1944)

per se can be ascribed to the specific metabolic action of these substances upon the heart muscle. In fact, the influence of the adrenosympathogenic neurohormones upon myocardial oxygen consumption constitutes the most serious biochemical threat to myocardial function and structural integrity, which can be expected of any endocrine action. Injection of epinephrine, as well as stimulation of the cardiac sympathetic nerves (nor-epinephrine discharges), is capable of enhancing myocardial oxygen consumption to such a degree that the accompanying active⁴¹ dilatation of the coronary arteries and augmentation of coronary blood flow^{41, 42, 101, 119, 119a, 171, 172, 229}

cardiac sympathetic nerves, despite simultaneously induced diminution of cardiac work and despite simultaneously increased coronary blood flow. This proves that the chemical oxygen-exhausting effect of sympathetic neurohormonal action takes place regardless of the magnitude of coronary flow and of the degree of cardiac muscular work. The finding of an elevated blood temperature in the coronary sinus, as compared with the temperature of the caval blood after injection of epinephrine and nor-epinephrine, plus indications of a simultaneous decrease of cardiac efficiency¹²⁷, as well as an augmentation of intramyocardial temperature¹²⁸, seem to point likewise toward an inadequate mechanical energetic utilization of oxygen, consumed during the action of adreno-sympathogenic neurohormones.

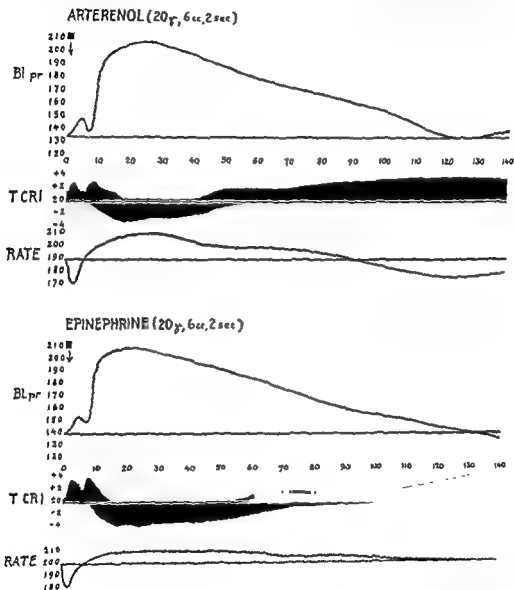
It has not been definitely decided whether the oxygen waste following epinephrine injection and nor-epinephrine action, is ultimately caused by adrenochrome^{176 271} or whether these amines act by themselves as oxidation catalysts^{272 273 274 275}. Be that as it may, the oxygen depletion of the heart muscle, which develops under the uncontrolled impact of epinephrine secretion and sympathetic neurohormonal discharges, must be considered as a singularly injurious interference in the metabolic equilibrium of the myocardial cells. It can hardly be over-emphasized as a phenomenon of fundamental significance for the understanding of various morbid states of the heart, and we shall have to refer to it on repeated occasions in the following deliberations. Acetylcholine and vagal stimulation exert an opposite, oxygen consumption-reducing and energy-saving effect on the heart muscle^{11 34 155 276 277} which is particularly marked counteracting the excess oxygen consumption under the influence of epinephrine¹¹⁰. Hence, the balance between sympathetic and vagal biochemical influences upon the myocardial metabolism must be considered as the decisive factor in . . .

epi . . . is a diminution of glycogen, creatinine, and adenylypyrophosphoric acid, plus an increase of lactic acid^{278 279 280 281}. The latter manifests itself by an acidification of the coronary venous blood¹¹⁰. No specific reports regarding the type of alterations produced by nor-epinephrine in the intermediate myocardial metabolism have been presented to date. The amount of extracellular water of the heart muscle is augmented by both epinephrine and nor-epinephrine²⁷⁹. Similar changes are elicited by general anoxia²⁸².

The serum potassium level is initially elevated and subsequently depressed by epinephrine^{280 282}. Nor-epinephrine acts in a similar manner^{280 282}.

The metabolic effects of the sympathomimetic catecholamines in the myocardium are reflected in deformations of the electrocardiographic T

2745, 3123, 3155, 3202 do not suffice to prevent exhaustion of the available oxygen, offered by the blood, which enters the coronary circulation^{830, 872, 916, 1199, 1199a, 1266}. This excessive oxygen consumption is an uneconomical and waste-



3. *Arterenol and cardio-acceleratory*
in the atro-
curves, see
1)

ful one in that it exceeds the oxygen utilization required to meet the demands of simultaneously increased myocardial dynamic performance^{830, 832, 916, 1199, 1199a, 2725} both in degree and duration¹¹⁸⁶. Eckstein et al⁸³² could even demonstrate myocardial hypoxia, resulting from stimulation of the

cardiovascular system can be postulated as a result of its stimulating effect upon the discharge of pituitary adrenocorticotrophic hormone (ACTH). This hormone, in turn, sets free adrenocortical steroids, some of which are apt to produce definitely injurious effects upon the blood vessels and the heart (see next section). Nor-epinephrine is very much less active in stimulating the pituitary adrenocortical system^{150, 162, 163, 210, 211, 212}.

SUMMARY. Epinephrine is prevailingly secreted by the adrenal medulla into the blood stream, while nor-epinephrine (essentially identical with sympathin), is prevailingly secreted by the postganglionic sympathetic fibers into their respective cardiovascular effector cells. Both are by far the most potent hormonal agents with rapid dynamic and metabolic action on the cardiovascular system. Apart from their pressor and heart-stimulating effects, they are capable, even in minute quantities, of causing severe myocardial hypoxia through direct chemical interference in myocardial metabolism, they give rise to an excessive, wasteful oxygen consumption by the heart muscle, which markedly exceeds the requirements for cardiac work, and which can exhaust the amounts of oxygen supplied even by an augmented coronary circulation (dilated coronaries). Thus they possess an unequalled importance as hypoxia-producing, potentially cardiotoxic, physiological chemical agents.

Vagal stimulation (acetylcholine liberation) exerts an opposite, oxygen-conserving effect upon myocardial metabolism, but acetylcholine is at the same time capable of liberating adrenergic catecholamines. The adrenergic-cholinergic biochemical interplay determines largely the metabolic and functional state of the heart muscle.

Morphogenic Effects

VASCULAR LESIONS The necrotizing and later calcifying lesions of the media layers of the aorta and other large arteries, which develop in rabbits after repeated injections of large doses of epinephrine, have been the subject of an extensive literature (reviewed by Hueper¹⁵⁶). Such lesions were also produced by the writer²⁶³ with adrenal extracts which contained lipid epinephrine compounds but no free epinephrine (Fig. 7). The fact is that

... with the manifestations of human arteriosclerosis. However, experiments with prolonged administration of small doses of epinephrine in rabbits and dogs have produced vascular lesions much like those of the human type, in that they were accompanied by marked fibrous thickenings of the intima and involved the large as well as smaller arteries^{272, 289, 1909, 2193}. Furthermore, it was found that the develop-

wave. Depressions of the T wave, probably due to hypoxia per se or to the accumulation of non-oxidized metabolites (lactic acid?), and elevations of the T wave, probably due to an excess of potassium, compete with each other and make their successive appearances after acute injections of epinephrine^{1962, 2463} (further lit. see Lepeschkin¹⁹⁶¹). Following inactivation of the vagus, the electrocardiographic effects of nor-epinephrine and of sympathetic stimulation are essentially the same as those elicited by epinephrine^{1962, 2703}. However, with the vagus reflexes functioning, nor-epinephrine produces, as a rule, an elevation of the T wave²⁷⁰¹. Adrenochrome in large doses elicits a depression of the T wave²⁷¹¹.

The "adrenolytic" drugs, mentioned in the preceding section on "hemodynamic effects" are much less potent in counteracting the cardiac chronotropic, inotropic and electrocardiographic manifestations of the sympathomimetic catecholamines (lit. see ²³³¹), although some of them (dihydroergotamine, SY30, dibenamine) proved capable of preventing the T wave depression to some extent¹⁹⁶³.

The most striking antagonistic action against the electrocardiographic T wave changes, provoked by epinephrine, nor-epinephrine, sympathetic stimulation and "sympathin" (largely nor-epinephrine extracted from the heart muscle), is exerted in the cat (but not in the dog²⁷¹³) by nitroglycerin^{27, 2709}. This and the partial suppression of adrenosympathogenic tachycardias through nitroglycerin^{2701, 2709} as well as the inhibition of oxidations by nitrites, which was observed in arterial tissue²⁷¹⁹, suggest a specific anti-adrenergic action of this drug on the heart muscle beside its well-known coronary dilator effect²⁷⁰⁹. An even more effective drug in counteracting epinephrine-induced cardiac acceleration is veratramine¹³²⁶.

The intensification of both physiological and toxic adrenergic actions on the heart under the influence of the thyroid hormone, will be dealt with in connection with the discussion of the latter hormone (p. 35 ff)

The rapidly fatal effect of large doses of epinephrine appears to be caused (except in the case of epinephrine-induced ventricular fibrillation^{1968, 2177}) by an acute exhaustion of myocardial oxygen and resulting cardiac standstill due to a coincidence of two toxic actions of epinephrine: (a) maximal wasteful myocardial oxygen consumption, initiated by excessive epinephrine concentrations, which have accumulated inside the heart muscle; and (b) respiratory failure²⁴³⁶ which, in addition, prevents adequate oxygenation of the blood²⁶⁹⁶. Whether the pulmonary edema, which often develops under the influence of large doses of epinephrine^{1341, 2101, 2170, 2290}, is caused mainly by acute left ventricular failure or by neurovegetative effects upon pulmonary capillary permeability, is still a matter of controversy^{1341, 2101, 2910}. L-nor-epinephrine was found to be less toxic in this respect²¹⁷⁰.

An indirect and slower detrimental influence of epinephrine upon the

cardiovascular system can be postulated as a result of its stimulating effect upon the discharge of pituitary adrenocorticotrophic hormone (ACTH). This hormone, in turn, sets free adrenocortical steroids, some of which are apt to produce definitely injurious effects upon the blood vessels and the heart (see next section). Nor-epinephrine is very much less active in stimulating the pituitary adrenocortical system^{134, 142, 162, 202, 214, 244}.

SUMMARY. Epinephrine is prevailingly secreted by the adrenal medulla into the blood stream, while nor-epinephrine (essentially identical with sympathin), is prevailingly secreted by the postganglionic sympathetic fibers into their respective cardiovascular effector cells. Both are by far the most potent hormonal agents with rapid dynamic and metabolic action on the cardiovascular system. Apart from their pressor and heart-stimulating effects, they are capable, even in minute quantities, of causing severe myocardial hypoxia through direct chemical interference in myocardial metabolism, they give rise to an excessive, wasteful oxygen consumption by the heart muscle, which markedly exceeds the requirements for cardiac work, and which can exhaust the amounts of oxygen supplied even by an augmented coronary circulation (dilated coronaries). Thus they possess an unequalled importance as hypoxia-producing, potentially cardiotoxic, physiological chemical agents.

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Morphogenic Effects

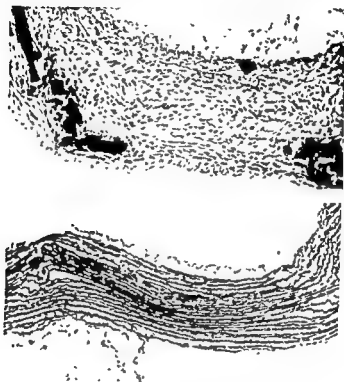
VASCULAR LESIONS. The necrotizing and later calcifying lesions of the media layers of the aorta and other large arteries, which develop in rabbits after repeated injections of large doses of epinephrine, have been the subject of an extensive literature (reviewed by Hueper¹²⁹). Such lesions were also produced by the writer²⁰¹ with adrenal extracts which contained lipid epinephrine compounds but no free epinephrine (Fig. 7). The fact that the intima remains intact in most instances and that also small vessels are unaffected as a rule, has been held against attempts to identify this "epinephrine sclerosis" pathogenically with the manifestations of human arteriosclerosis. However, experiments with prolonged administration of small doses of epinephrine in rabbits and dogs have produced vascular lesions much like those of the human type, in that they were

markedly different in their

small

ment of atheromatous deposits in the intima of cholesterol-fed rabbits is strikingly accelerated and intensified by injections of epinephrine^{59, 660, 1522} and by epinephrine-lipid compounds extracted from the adrenal glands²⁶⁶⁴ (Fig. 8). Likewise, extracts made from the serum of arteriosclerotic and hypertensive patients and containing lipid-bound epinephrine¹⁵¹⁷ accelerated the cholesterol atheromatosis in rabbits²⁶⁶⁴ (see Fig. 27).

Castration has been claimed to intensify²⁰²⁶, ergotamine to prevent¹⁹¹³



5 weeks

(After W Raab, Ztschr f exp Med 103 657, 1939)

epinephrine sclerosis. Whether endarteritis-like alterations of the peripheral arteries, which were observed after repeated implantations of adrenal tissue^{1574, 1970, 2188}, are to be ascribed to the effects of epinephrine or of cortical steroids or to their combined action, remains to be clarified.

As regards the mechanism by which epinephrine causes vascular lesions, various theories have been advanced: constriction of the small nutritive vessels of the larger vessel walls with resulting disturbances of the local blood supply¹⁹⁰⁹; obliterating endothelial proliferation of the vasa vasorum^{2443, 2493}; metabolic alterations of the vascular protein composition, which also facilitate the deposition of calcium³⁰²⁷.

Arterial tissue was found to absorb epinephrine *in vitro*³⁵⁴, and the presence of epinephrine-like catecholamines in vascular walls was demonstrated biologically^{169, 2017} and chemically²⁶⁷³. Since one of the outstanding metabolic effects of epinephrine is the excessive local consumption of oxygen, leading to tissue hypoxia^{267, 216, 2199, 222, 229, 232}, and since hypoxia *per se* was seen to elicit degenerative calcifying lesions in the rabbit aorta¹²⁴ and in the cerebral arteries of cats³⁴⁵, the writer would favor the conception

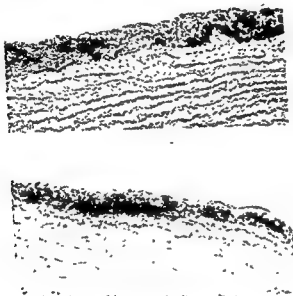


FIG. 2. Thrombosis in aorta.

that the injurious effect of epinephrine on the arterial walls is essentially a direct chemical one, caused by the local hypoxia-producing action of epinephrine.

The significance of nor-epinephrine as the physiological chemical neurotransmitter of the sympathetic nervous system was recognized only in recent years. No studies concerning morphogenic effects of the artificial administration of this important substance have been published as yet. However, in consideration of the neurosecretory, nor-epinephrine-discharging function of the sympathetic nervous system^{265, 2797} and of the presence of considerable quantities of catecholamines in the arterial walls^{2673, 2017}, it

appears justified to interpret morphogenic effects, resulting from local sympathetic stimulation, as being due essentially to nor-epinephrine, discharged by the postganglionic sympathetic fibers into their vascular effector cells. The nor-epinephrine concentration in the media is higher than in the intima³⁰¹⁷. A local hypoxia-producing effect of sympathetic stimulation, analogous to that of injected epinephrine, was proven at least for the heart muscle^{230, 1139a}; also the general oxygen consumption was found to be increased by nor-epinephrine^{731, 1936}, although to a lesser extent than by epinephrine^{2106a}.

Electrical stimulation of vascular walls was reported as being followed by necrotizing lesions of the media, analogous to those elicited by epinephrine¹⁹⁰⁹. Injection of sympathetic stimulating nicotine produced identical vascular changes³⁰¹⁸. The administration of nicotine, like that of epinephrine, intensified cholesterol atheromatosis in the rabbit⁶⁶⁰. In cholesterol-fed animals, degenerative changes were observed in the sympathetic ganglia⁶⁶⁰. Physical exercise (treadmill), which is associated with stimulation of the cardiac sympathetic nerves, produced marked sclerosis of the coronary arteries in cholesterol-fed animals³⁰¹⁵.

Since renal excretory insufficiency is accompanied by the accumulation of sympathomimetic catecholamines in the blood²⁶⁷⁴, it seems possible that the severe necrotizing vascular lesions, which develop in animals with experimental excretory insufficiency of the kidneys¹¹⁷³, may be caused by these excessive quantities of circulating angiotoxic material.

CARDIAC LESIONS. The injection of large doses of epinephrine is immediately followed by a dilatation of the heart and by an extra- and intracellular accumulation of water in the myocardium²³²¹. After repeated injections of epinephrine, the development of myocardial hypertrophy was reported^{173, 1301, 1643, 3274}, together with degenerative changes in the heart muscle, ranging from hyaline degeneration to necroses and scar formation^{1004, 1071, 1858, 2345} (for older literature, see ²⁶⁷⁰). Such cardiac lesions were also noted in an asthma patient, who had been treated for years with large doses of epinephrine¹⁰³⁷. They were found greatly enhanced by the simultaneous administration of thyroid hormone¹³⁰¹.

No studies on the morphogenic effects on the heart, exerted by nor-epinephrine injection or by direct sympathetic nerve stimulation, have come to the attention of the writer, but he has observed the accumulation of epinephrine-like catecholamines (probably largely nor-epinephrine^{1296, 1858, 2710}) in the heart muscle of the cat and rat after electrical stimulation of the cardiac sympathetic nerves²⁷⁰² and after physical exercise²⁶⁴², which is known to elicit sympathetic discharges. Myocardial necroses were produced by faradization of intact animals¹⁵²¹.

It appears most likely that the myocardial lesions, perhaps also the cardiac hypertrophy, produced by epinephrine and sympathetic stimulation, are directly or indirectly attributable to the local hypoxia-producing effect of the sympathomimetic catecholamines. The stimulation of nor-epinephrine-discharging cardiac sympathetic nerves causes myocardial hypoxia^{130, 132, 1193}. Disseminated necroses¹³³ and cardiac hypertrophy (lit., see ²⁶⁷) were observed in animals after enforced strenuous exercise¹³².

Acetylcholine is a physiological stimulant of adrenergic neurosecretion^{113, 617, 963, 1011}, apart from its "muscarinic" vagal action. Accordingly, its frequent injection produces myocardial degenerative changes, analogous to those elicited by epinephrine^{1337, 1441}.

Sympathectomy, which leads to a marked decrease of the catecholamine concentration in the heart muscle^{2714, 13084}, is often followed by a reduction of the heart size^{1216, 1231}.

Whether the cardiac hypertrophy and coronary sclerosis of cholesterol-fed rabbits^{1015, 1718} is caused directly by the cholesterol which accumulates in the heart¹⁶¹⁵ or indirectly by cholesterol-induced degenerative alterations in the sympathetic ganglia⁶⁰⁸, cannot be decided at present.

SUMMARY. Over-dosage of epinephrine and sympathetic stimulation (i.e., neurosecretory discharges of nor-epinephrine) are capable of producing necrotic calcifying lesions in the media of the large vessels. The formation of intima lipoidosis (atheromatosis) is markedly intensified by epinephrine and by sympathetic stimulation.

Cardiac hypertrophy, degenerative changes of the myocardium and coronary sclerosis can be elicited by both epinephrine and sympathetic stimulation.

All these forms of vascular and cardiac structural lesions may be attributable to the local metabolic action of epinephrine and nor-epinephrine, especially to their chemical hypoxia-producing property.

appears justified to interpret morphogenic effects, resulting from local sympathetic stimulation, as being due essentially to *nor*-epinephrine, discharged by the postganglionic sympathetic fibers into their vascular effector cells. The *nor*-epinephrine concentration in the media is higher than in the intima³⁰¹⁷. A local hypoxia-producing effect of sympathetic stimulation, analogous to that of injected epinephrine, was proven at least for the heart muscle^{330, 1199*}; also the general oxygen consumption was found to be increased by *nor*-epinephrine^{733, 1956}, although to a lesser extent than by epinephrine^{2106*}.

Electrical stimulation of vascular walls was reported as being followed by necrotizing lesions of the media, analogous to those elicited by epinephrine¹⁹⁰⁹. Injection of sympathetic stimulating nicotine produced identical vascular changes³⁰¹⁶. The administration of nicotine, like that of epinephrine, intensified cholesterol atheromatosis in the rabbit⁶⁶⁰. In cholesterol-fed animals, degenerative changes were observed in the sympathetic ganglia⁶⁶¹. Physical exercise (treadmill), which is associated with stimulation of the cardiac sympathetic nerves, produced marked sclerosis of the coronary arteries in cholesterol-fed animals³⁰¹⁵.

Since renal excretory insufficiency is accompanied by the accumulation of sympathomimetic catecholamines in the blood²⁶⁷⁸, it seems possible that the severe necrotizing vascular lesions, which develop in animals with experimental excretory insufficiency of the kidneys¹¹⁷², may be caused by these excessive quantities of circulating angiotoxic material.

CARDIAC LESIONS The injection of large doses of epinephrine is immediately followed by a dilatation of the heart and by an extra- and intracellular accumulation of water in the myocardium²⁴²¹. After repeated injections of epinephrine, the development of myocardial hypertrophy was reported^{175, 1301, 1633, 2276}, together with degenerative changes in the heart muscle, ranging from hyaline degeneration to necroses and scar formation^{1004, 1621, 1636, 2543} (for older literature, see ²⁶⁷⁰). Such cardiac lesions were also noted in an asthma patient, who had been treated for years with large doses of epinephrine¹⁰³⁷. They were found greatly enhanced by the simultaneous administration of thyroid hormone¹³⁰¹.

No studies on the morphogenic effects on the heart, exerted by *nor*-epinephrine injection or by direct sympathetic nerve stimulation, have come to the attention of the writer; but he has observed the accumulation of epinephrine-like catecholamines (probably largely *nor*-epinephrine^{1206, 1553, 2710}) in the heart muscle of the cat and rat after electrical stimulation of the cardiac sympathetic nerves²⁷⁰² and after physical exercise²⁶³², which is

as a conveniently available, but also as a functionally representative member of the mineralocorticoid group. Many experimental results, obtained with either desoxycorticosterone acetate (DCA) or desoxycorticosterone glucoside (DCG), are being regarded as valid equivalents of cortical function. Despite the water-solubility of DCG, its biological activity is considerably less potent than that of the fat-soluble DCA^{101, 120}. The salt-retaining effect of 17-hydroxy-11-desoxycorticosterone (compound S) is

workers⁶⁷, suggests the possibility that the number of different biologically active steroids, produced by the adrenal cortex, has been over-estimated. 17-hydroxycorticosterone was found by these workers to combine the effects of desoxycorticosterone, a typical "mineralocorticoid", and of cortisone (compound E, 11-dehydro-17-hydroxycorticosterone), a typical "glucocorticoid". Furthermore, 17-hydroxycorticosterone (compound F) evoked all the reactions otherwise elicited by the administration of ACTH as well as an increased excretion of 17-ketosteroids. If the contention that compound F is "the" adrenal cortical hormone, elaborated by the normal cortex⁶⁷, should prove correct, this would simplify matters; but it seems still too early to abandon the customary, although somewhat arbitrary, separate consideration of mineralo- and glucocorticoids, which proved useful in the interpretation of various clinical manifestations and which will be adhered to in the following.

HEMODYNAMIC EFFECTS OF MINERALOCORTICOID. During administration of DCA, a gradual elevation of the blood pressure, which often reached outright hypertensive levels, was observed by numerous investigators in animals and human subjects (literature, see 190, 210, 226, 227) with about equal participation of the systolic and diastolic pressures^{204, 221, 222}. DCA favors also the development of hypertension in animals with experimental perinephritis⁷⁹ and in nephrectomized animals¹⁰². Only few workers^{191, 211} failed to produce DCA hypertension in dogs and rats. Large doses of DCA are apt to elicit irreversible elevations of the blood pressure^{101, 122}. This "self-sustaining post-DCA hypertension"¹²² is paralleled by certain morphological cardiovascular lesions, especially of the kidneys (p. 31), and its mechanism appears to be fundamentally different from that of the DCA-induced hypertension in the developing stage. The mechanism of the

Adrenocortical Hormones

In contrast to the rapidly arising and vanishing metabolic and dynamic phenomena, provoked by the sympathomimetic amines in the cardiovascular system, the effects which are called forth by some of the cortical steroids develop at a very much slower pace and may take days or weeks to become discernible. It is, therefore, assumed by many workers that certain cardiovascular manifestations, usually caused by cortical steroids, are not the result of a direct hormonal action on the contractile elements, but secondarily elicited through primary general metabolic and renal functional changes, especially concerning the electrolyte balance.

The cortical "glucocorticoids" and "mineralocorticoids" exert influences upon the heart and blood vessels, which differ greatly in degree and quality but which overlap in various respects. Beside these overlappings of function, it must be kept in mind that certain antagonisms seem to be operating between the activities of some of the cortical steroids^{891, 2194a, 3093}. These mutual interferences may possibly be mediated in part through the quantitatively varying inhibitory effects of the individual corticoids²⁹⁵⁴ upon the anterior lobe of the pituitary, which, by means of its corticotrophic hormone (or hormones?), governs the secretion of all the biologically active cortical steroids²⁹⁵². Furthermore, the differential inactivation of adrenal corticoids by the liver may be an important factor in the functional effects of adrenal cortical secretion^{931, 1215}.

It is still an open question whether the ability of epinephrine to initiate the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary is to be interpreted as a direct specific action of epinephrine upon the pituitary^{1919, 2052, 2131} or as an unspecific "stress" phenomenon, resulting in a corticoid depletion of the body fluids and a corresponding uninhibited release of ACTH^{2952, 2954}. Recent observations make a predominant role of epinephrine as the only specific activator of the pituitary-adreno-cortical complex doubtful²⁹².

Functional Effects

Mineralocorticoids

Among the cortical steroids, the "mineralocorticoids" are the ones endowed with the most striking cardiovascular effectiveness of a potentially harmful nature. Desoxycorticosterone, although probably present in the adrenal cortex²⁷⁸¹ in only small amounts, is generally considered not only

ternal environment", created by enhanced intracellular accumulation of sodium in the tissues^{444, 985, 1112, 1574, 2335, 2529, 2651, 2691a}, regardless of the fact that the water retention during administration of DCA is only a transient phenomenon^{1214, 2341, 2705} and that an elevation of the serum sodium level¹⁶⁴² does not regularly occur^{2571, 2705}. An extrarenal mechanism of the DCA-induced hypertension is also suggested by its occurrence in nephrectomized animals¹⁰⁷⁷. The lack of a constant increase of plasma volume under the influence of DCA²⁵⁷² and of a clear-cut time coincidence between existing plasma volume augmentations^{255, 965} and blood pressure elevation^{2571, 2572} is not incompatible with an increased deposition of sodium inside the contractile elements of the cardiovascular system. The latter seems to constitute an essential feature for elevation of the pressure. Intracellular accumulation of sodium under the influence of DCA has been demonstrated for the heart muscle^{644, 2529} and the skeletal muscle^{965, 1574, 2231, 2691} and as a general phenomenon^{651, 1112}, while the sodium concentration of the musculature^{678a} and of the heart muscle in particular^{445, 2529} was found diminished after adrenalectomy. The effect of DCA upon the sodium concentration of the arteriolar muscular cells has not yet been investigated but the arterial walls of hypertensive individuals proved to contain abnormally large quantities of sodium²⁴¹⁵. The total body sodium of renal hypertensive rats was likewise found to be markedly increased. Since the plasma sodium concentration was normal, it was concluded that the excess sodium is deposited intracellularly^{2305a}.

Observations suggesting that the hypertensive effect of DCA can be prevented by a drug (phenergan), which is supposed to reduce the cell membrane permeability for sodium¹²¹⁷, seem to be consistent with the above outlined concept.

The characteristic loss of potassium from tissues and serum under the influence of DCA^{2136, 2590, 2541, 2704} may be an additional contributory factor in the hypertensive action of DCA whose influence on selective membrane permeability for electrolytes appears to constitute a decisive element in cardiovascular cell contractility^{1221a}.

A phenomenon which appears particularly significant in evaluating the mechanism of DCA-induced elevations of the blood pressure, is the intensification of the pressor effects of both epinephrine^{2495, 2704, 2912} and nor-epinephrine^{2094, 2704} in normotensive human subjects after treatment with DCA (Fig. 9). On the other hand, the pressor effect of epinephrine^{2776, 2841, 2770, 2497} and nor-epinephrine²⁷²³ was reported weakened in conditions of adrenal cortical under- or non-function. In hypertensive patients^{250, 1150, 1251, 1404} and in animals, made hypertensive through DCA²²⁴, the pressor effect of epinephrine did not appear regularly increased; but the pressor efficiency of nor-epinephrine proved greater in hypertensive individuals

nervous system and the kidneys rather than the adrenal cortex are responsible for the maintenance of the "post-DCA hypertension".

Adrenalectomy, on the other hand, is followed by absolute arterial hypotension in originally normal animals and by a lowering of the blood pressure in animals with renal hypertension (literature, see 564, 1009, 1400, 2500, 2565, 3537a, 3724), or with hypertension produced by total nephrectomy¹⁰⁰⁸ or with centrogenic forms of hypertension^{1653, 2120}. The hypertension which follows combined bilateral nephrectomy and adrenalectomy may persist for weeks until a state of advanced adrenal insufficiency sets in²⁴³³. Its occurrence proves that intact adrenal function is not indispensable for the type of hypertension which results from renal excretory insufficiency and which may possibly be ascribable to the retention of otherwise excreted adrenal corticoids and sympathogenic pressor catecholamines in analogy to conditions prevailing in clinical uremia (p 312, 479). The pressor response to injected epinephrine²⁷⁷⁶, nor-epinephrine^{1000, 2733}, pitressin, neosynephrine, privine²⁷⁷⁶, renin^{693, 1063, 2777} and to nervous stimulation^{2776, 3061} is reduced after adrenalectomy, and the formation of the vascular sensitizing agent VEM is impaired^{3123, 3124, 2726}. A normally reacting blood pressure level, all the above-named pressor reactions and the formation of VEM can be restored through the administration of DCA^{2496, 2777}. On the other hand, no increase of VEM formation was observed in rats, made hypertensive through DCA, so that this type of hypertension does not appear to be caused by an excess of VEM²⁷²⁶.

Hypophysectomy prevents the DCA-induced elevations of the blood pressure and, as already mentioned, abolishes the post-DCA hypertension^{1232b}. Since the latter could not be restored by ACTH^{1232b}, it seems that it is not the adrenocorticotrophic function of the pituitary whose integrity is necessary for the persistence of the "self-sustaining post-DCA hypertension".

There can hardly be any doubt left that sodium plays an important part in the pressor mechanisms, which are set into motion by the mineralocorticoids, and by DCA in particular. The simultaneous administration of DCA and sodium chloride distinctly intensifies the vasopressor effect of DCA^{1076, 1247, 1303, 1792, 2244, 2943}, while deprivation of sodium diminishes it^{2563, 2570, 2690, 2943, 3092, 3226}. It is believed by some workers^{1292, 2563, 2573, 2943} that excessive intake of sodium chloride per se will not cause a significant elevation of the blood pressure, but a number of other experimental observations^{371, 1200, 2993} disprove this view. Apparently any pressor action of sodium chloride is dependent on the support by adrenal mineralocorticoids²⁵⁷⁶. Considering the tendency of DCA to retain sodium in the body^{779, 1112, 1747, 2371, 3391}, it can be assumed as a logical possibility that the delayed pressor effect of DCA might be called forth by the gradual alteration of the "in-

ternal environment", created by enhanced intracellular accumulation of sodium in the tissues^{664, 369, 112, 124, 223, 270, 361, 361a}, regardless of the fact that the water retention during administration of DCA is only a transient phenomenon^{124, 361, 373} and that an elevation of the serum sodium level³⁶¹ does not regularly occur^{271, 274}. An extrarenal mechanism of the DCA-induced hypertension is also suggested by its occurrence in nephrectomized animals³⁷¹. The lack of a constant increase of plasma volume under the influence of DCA²⁷³ and of a clear-cut time coincidence between existing plasma volume augmentations^{371, 373} and blood pressure elevation^{271, 273} is not incompatible with an increased deposition of sodium inside the contractile elements of the cardiovascular system. The latter seems to constitute an essential feature for elevation of the pressure. Intracellular accumulation of sodium under the influence of DCA has been demonstrated for the heart muscle^{361, 370} and the skeletal muscle^{364, 375, 313, 369} and as a general phenomenon^{63, 112}, while the sodium concentration of the musculature³⁷⁶ and of the heart muscle in particular^{63, 370} was found diminished after adrenalectomy. The effect of DCA upon the sodium concentration of the arteriolar muscular cells has not yet been investigated but the arterial

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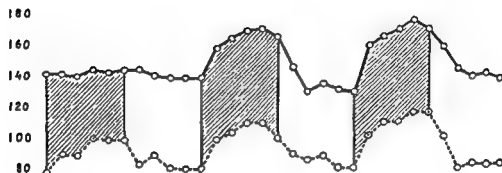
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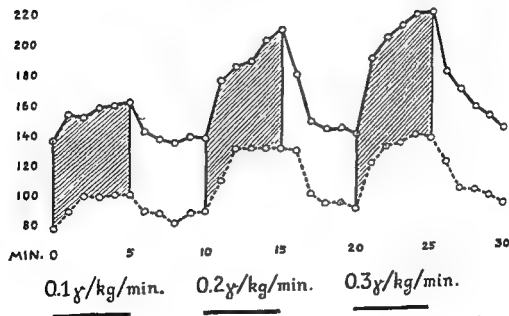
... through DCA³⁷¹, the pressor effect of epinephrine did not appear regularly increased, but the pressor efficiency of nor-epinephrine proved greater in hypertensive individuals.

than in normals^{1150, 2335}. It is noteworthy that the "sensitization" of the cardiovascular system to sympathomimetic pressor effects through desoxy-

NOR-EPINEPHRINE (ARTERENOL) INFUSIONS BEFORE DCA



AFTER DCA (18 DAYS, 10 mg each)



corticosterone does not take place immediately^{2712, 2913, 3055, 3112}, possibly because it depends on the time-consuming process of sodium deposition in the tissues^{661, 961, 1112, 1231a, 1274, 2920, 3651}. Recent observations of the writer

and his associates²⁷⁰ revealed an absence of the enhancing effect of DCA upon the weakened action of epinephrine and nor-epinephrine in humans during periods of sodium withdrawal.

All these findings suggest the hypothesis that the hormone-regulated concentration of sodium, which is present in the muscular cells of the cardiovascular system at a given time, determines the maximal contractile responsiveness of these cells to adequate stimuli.

Some evidence in favor of this hypothesis is available in findings of Fleckenstein^{100, 102}, obtained on frog muscles, which show that the amplitude of muscular contraction depends on the magnitude of the electric membrane potential which, in turn, is determined by the concentration difference between extra- and intracellular sodium and potassium ions. Fleckenstein¹⁰² assumes that this ionic concentration difference, and with it the electrical membrane potential, will rise under the influence of DCA and fall in the absence of mineralocorticoids. It seems probable, therefore, that DCA, by increasing the membrane potentials of the catecholamine-sensitive vascular muscle fibers, augments the contractile effect which is elicited by epinephrine and nor-epinephrine through their depolarizing action¹²⁸. The latter type of action was also observed on the striated muscle of the cat with epinephrine, nor-epinephrine and sympathetic stimulation¹³⁴ and on the heart with epinephrine¹³⁵. Hence, the hypertensive effect of DCA seems to be due essentially to an accentuation of the pressor efficiency of normal quantities of intrinsic vascular nor-epinephrine, brought about by the DCA-induced deposition of extra sodium in the vascular walls. Ingestion of extra sodium chloride would further intensify this process provided the

amount is proportion to both the amounts of available sympathomimetic stimulating material (intrinsic catecholamines) and of available response-permitting material (intracellular sodium). Functional relations of this kind would also make intelligible the hemodynamic peculiarities of adrenalectomized animals and hypoadrenocortical humans: a low vascular tone and a diminished response to various pressor stimuli (carotid sinus reflex¹⁴², cerebral ischemia¹⁴³), which are mediated by sympathetic neurohormonal discharges, and to renin injections^{100, 117, 141}. Sodium depletion of the arterial walls, due to absence of mineralocorticoids, would have to be considered as having diminished the maximal cellular contractile responsiveness. On the other hand, the failure of DCA to raise the blood pressure during salt withdrawal^{144, 145, 146} and to restore the weakened pressor effects of epinephrine and nor-epinephrine²⁷⁰, would have to be explained as the result of a lack of the chemical intermediary (sodium), through which DCA otherwise enables the sympathomimetic neurohor-

mones, acting upon the vascular muscle cells, to elevate and to maintain the blood pressure level.

Although the sodium ion occupies a prominent place in the biological effects of the mineralocorticoids and although much emphasis is given its role in cardiovascular pathology, it should be understood that the demonstrable changes in sodium metabolism represent only one partial aspect of the alterations of electrolyte equilibrium, which contribute to modifications of the presumably decisive factor, namely, the difference between total intra- and extracellular electrolyte concentrations as the determinant of the electrical cell membrane potential. This is illustrated by the observation that the blood pressure is reduced and the pressor efficiency of epinephrine and nor-epinephrine weakened by withdrawal not only of sodium but also of potassium, while combined restriction of both ions was found to prevent the depressor effect of potassium depletion¹⁰⁷⁰, possibly through maintenance of a nearer normal intra-extracellular electrolyte equilibrium.

DCA, on the other hand, was found to accentuate the depressor effect of potassium deprivation, probably by a further active depletion of intracellular potassium, while the feeding of extra potassium rendered the pressor action of DCA per se more intense and more persistent than the feeding of extra sodium.^{1073a, 2492a}

All this tends to prove the fundamental role of the electrolyte equilibrium in the mechanism of electrophysical blood pressure regulation. The alimentary electrolyte intake as well as the intra-extracellular electrolyte exchange in the cardiovascular tissues under the influence of the corticoids, and the resulting alterations of muscular contractile responsiveness to depolarizing pressor agents (notably the sympathomimetic catecholamines) appear as dominant factors in the maintenance and reactivity of vascular tone.

CARDIAC EFFECTS OF MINERALOCORTICOIDS. Despite the well-known occurrence of cardiac enlargement, congestive failure^{969, 2129, 2133, 2561, 2616} and myocardial degenerative changes^{884, 2047} as sequelae of an over-dosage of DCA, comparatively little work has been done to date concerning the nature of the influence of DCA and other mineralocorticoids upon the heart muscle.

In acute experiments with intravenously applied DCG (water soluble desoxycorticosterone glucoside), the cardiac output was slightly decreased¹²¹⁹, no alterations of the myocardial glycogen and lactic acid were observed³⁰³⁵, but if injected simultaneously with epinephrine, DCG was found to prevent the loss of glycogen, the increase of lactic acid, and the electrocardiographic changes otherwise elicited by epinephrine²⁰⁵⁵. This was interpreted as indicating a protective rather than a potentially injurious

effect^{30,35} In adrenalectomized animals, the decreased rate of phosphorylation of glycogen is restored by DCA^{32,33}.

However, the gradually developing changes of the myocardial intracellular electrolyte pattern which are elicited by the administration of excess DCA seem to offset in the end whatever direct influence it might have exerted initially upon the myocardial metabolism. An intracellular accumulation of sodium^{65, 75, 86, 118} and a less conspicuous depletion of potassium (the latter especially under a low potassium regime^{65, 86}) are characteristic effects of DCA over-dosage upon the heart. Conversely, adrenalectomy is followed by a decrease of sodium and an increase of potassium in the myocardium^{65, 75}, but the efficiency of DCA in accumulating intracellular sodium in the heart muscle is even more marked in adrenalectomized than in normal animals^{74, 75} in keeping with the rule that mineralocorticoid action is intensified in the absence of glucocorticoids.

Depressions of the S-T segment and flattening or inversion of the T wave were observed both in dogs¹⁵⁵ and humans²⁴⁴ but may fail to appear (lit., see ¹⁹⁶). The electrocardiographic alterations, provoked by injection of epinephrine and by exercise, became slightly accentuated after pre-treatment with DCA^{275, 276}. The heart rate was not significantly influenced^{164, 275}.

In experimental adrenal insufficiency the electrocardiogram is also apt to show certain abnormalities^{23, 264}, which may be explained in part as the result of toxic potassium concentrations in the serum and the heart muscle itself^{65, 364}.

In the isolated frog heart, the inotropic action of epinephrine was found intensified by DCA²⁷², and the dynamic weakness of the heart of animals with cortical insufficiency¹⁶⁷ could be corrected by medication with DCA²⁴¹. Perfusion experiments with cortical extracts and with suprarenal venous blood on isolated mammalian hearts did not yield any conclusive results⁷⁹. Recent investigations by Haydu and Szent Györgyi²⁴⁶ make it probable that DCA acts on cardiac muscular contractility by modifying "the selective activity of the membrane by which this organ decides the composition of the intracellular ionic atmosphere and governs herewith the behavior of actomyosin."

Glucocorticoids and Adrenal Cortical Extracts

The so-called glucocorticoids of the adrenal cortex, four of which are chemically identified as carrying an oxygen atom on carbon atom 11 (11-oxy-steroids), bear their name because of the prominent role they play in carbohydrate metabolism. It consists especially of the conversion of proteins into carbohydrates, deposition of glycogen in the liver and inhibi-

tion of carbohydrate utilization¹⁸²⁶. Furthermore, the glucocorticoids promote the breakdown of lymphoid tissue and immobilization of circulating eosinophils in the bone marrow^{2396, 2585}. Some of them exert a strongly inhibiting effect upon the production and secretion of the adrenocorticotrophic hormone (ACTH) by the anterior pituitary²⁹⁵⁴.

In the following, we shall refer to effects produced in the cardiovascular system by certain individual glucocorticoids wherever such data are available, but also to less specific composite effects brought forth either by not quite clearly defined mixtures of cortical steroids, including glucocorticoids, or, on the other hand, by adrenalectomy which involves all cortical compounds.

HEMODYNAMIC EFFECTS OF GLUCOCORTICOIDS AND CORTICAL EXTRACTS

Compound E (cortisone) was found to elevate the blood pressure to some extent, especially in adrenalectomized nephritic rats¹⁷⁹³ and in Addison's disease²³⁷⁵, but its effect on the blood pressure of normal animals¹⁷⁹³ and human subjects was not striking^{1460, 2585, 2596}. The more marked pressor response of animals and humans with absent or non-functioning adrenals was interpreted as being due either to the lack of other antagonistic cortical steroids¹⁷⁹³ or of a hypothetical cortisone-inactivating function of the adrenals¹⁸²⁷. A certain influence of cortisone upon the inherent tone of the vascular contractile cells is suggested by the observation that it elevates the blood pressure "floor", which becomes manifest during action of the ganglionic blocking agent tetraethylammonium chloride¹⁴⁶. In human subjects, cortisone was not found to significantly counteract the potentiation of the pressor effect of epinephrine by DCA. The potentiation of the nor-epinephrine effect was only slightly weakened^{2721a}.

Like 17-hydroxycorticosterone^{779, 1629, 2292}, cortisone promotes the excretion of sodium by animals and man^{651, 1460, 2292} temporarily but was found to cause retention of sodium in patients with Addison's disease¹⁰¹⁹. Water is retained in the body under the influence of cortisone, but only during the beginning of its administration, and existing edema may even be removed by it¹⁴⁶⁰.

A number of other steroids were also investigated with regard to their pressor effectiveness. The results were contradictory (lit. see ²⁵⁶⁵) and do not need to be discussed here in detail.

Adrenocortical extracts with no clearly defined chemical composition were reported as not exerting any significant pressor effect in normal animal and humans^{1115, 1166, 1299, 1795}. However, they are able to restore the lowered blood pressure of adrenalectomized rats to normal or even hypertensive levels²⁰⁰³. In one human subject, the administration of "cortin" together with sodium chloride produced severe hypertension⁴⁶. On the other

hand, the blood pressure of hypertensive rats⁴⁵⁴ and of animals, made hypertensive by DCA¹⁶⁵⁷, was lowered through cortical extracts. Similarly, ascorbic acid was found to prevent and abolish DCA-induced hypertension in intact, but not in adrenalectomized rats¹⁶⁷¹, presumably via new formation of glucocorticoids.

The constrictor response of isolated vessels to epinephrine appeared enhanced by cortical extracts²⁹²⁵ and that of the splanchnic vessels to nor-epinephrine by 11-oxysteroids^{1690, 2732}. An analysis of the peripheral hemodynamic effects of cortical preparations revealed such a close similarity with those produced by physiological doses of epinephrine that functional relationships between adrenal medullary and cortical vascular effects have to be suspected also regarding corticoids other than DCA¹⁶⁵⁰. The demonstration of the existence of lipid-epinephrine compounds with a pressor effectiveness greater than that of epinephrine per se^{1615, 1716}, the intimate vascular connections between adrenal cortex and medulla¹⁶⁰⁰ and the histologically visible migration of cortical lipoidal substances toward the medulla^{216, 2670}, suggest the possibility of functionally important physical and chemical linkages between epinephrine and certain cortical lipids. Up to the present, such a compound formation with catecholamines has been proven regarding locithin^{1716, 2116, 2673}, but not regarding hormonal corticoids²⁶⁷⁴.

As far as interference of cortical extracts in electrolyte metabolism is concerned, no characteristic behavior of the serum sodium and potassium levels^{2974, 4672} was reported in normal animals, but the DCA-induced hypernatremia was diminished by cortical extracts³⁶⁶². This was interpreted³⁶⁶² as suggesting that the over-all secretion of the adrenal cortex tends to maintain normal electrolyte levels both against the specific sodium-retaining influence of DCA on one hand, and against sodium loss on the other.

The lowering of the blood pressure level and the decrease or abolition of the response to various pressor stimuli after adrenalectomy (p. 22) are probably not ascribable exclusively to the lack of mineralocorticoids but also to that of the glucocorticoids. This is suggested by the possibility to restore the blood pressure to or above normal through treatment with mixed adrenocortical extracts^{2312, 2703} and cortisone¹⁶¹¹. The pressor and local vasoconstrictor effectiveness of nor-epinephrine, which is largely lost in adrenalectomized animals, can be rapidly restored by injection or topical application of cortisone¹⁶¹¹. The pressor effect is probably by virtue of their

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CARDIAC EFFECTS OF GLUCOCORTICOIDS AND CORTICAL EXTRACTS. An augmentation of the contractile force of the heart through adrenocortical extracts was observed by several investigators in the frog^{1100, 1103, 2752, 2255}, but not in mammals²¹⁹⁰. This discrepancy may possibly be explained by the fact that the frog heart, in contrast to the mammalian heart, contains pure epinephrine²⁰⁷⁷ and that the epinephrine sensitivity of the heart was found to be increased by adrenocortical extracts^{80, 2722, 2752} and by certain lipids¹⁴¹¹. This latter phenomenon has been ascribed to a "stabilization" of epinephrine¹⁴¹¹. On the other hand, cardiac efficiency appeared depressed following adrenalectomy^{331, 1029} but could be restored to normal through adrenocortical extracts³³¹. In contrast to DCA, cortisone did not influence the contractility of the frog heart^{1331a}.

The heart rate does not seem to be significantly affected by adrenocortical extracts²¹⁹⁰, nor was any major influence upon the coronary flow observed^{2403, 2490}.

Adrenalectomy may be followed by bradycardia²¹, electrocardiographic abnormalities (depression of S-T and inversion of T, low voltage²¹) and, rarely, by auricular fibrillation²⁴¹⁹. These changes can be normalized through application of adrenocortical extracts²¹. One could consider the possibility that the "hypoxic" electrocardiograms in adrenal insufficiency might be caused by an inability of the heart muscle to utilize oxygen, which would lead to an accumulation of unoxidized metabolites in the myocardium. An interference of adrenalectomy in oxidative processes was observed by several investigators^{1193, 1543, 2906, 3412}. Its influence on cardiac electrolytes was mentioned on p. 23.

The myocardial glycogen stores were found diminished in adrenalectomized animals^{339, 1235, 3061}, whereas the adenosinephosphoric acid^{1438, 3051} and creatine phosphoric acid^{2107, 3051} of the heart muscle do not seem to be characteristically altered by adrenalectomy.

SUMMARY The mineralocorticoids (11-desoxycorticosterone and related compounds) are capable of producing striking cardiovascular effects, especially as slow acting regulators of the blood pressure level. They participate significantly in the maintenance of the pressor efficiency of the sympathomimetic amines, epinephrine and nor-epinephrine, and, if present in excess, augment the pressor effect of these catecholamines. These phenomena seem to depend on the ability of the mineralocorticoids to deposit sodium intracellularly and thus to augment the electric membrane potential of the contractile cells of the cardiovascular system. Prolonged excessive action of the mineralocorticoids, particularly in the presence of extra amounts of sodium, can lead to self-sustained, persistent arterial hypertension and congestive heart failure.

The glucocorticoids (e.g., cortisone) produce some similar, though weaker, effects on the cardiovascular system, but may, under certain circumstances, counteract the sodium-retaining and pressor action of the mineralocorticoids. They seem to share with the latter the ability to maintain vascular constrictor responsiveness to nor-epinephrine and thus to safeguard cardiovascular homeostasis. However, the mechanism of their action differs from that of the mineralocorticoids in that it is more rapidly effective and, apparently, not primarily concerned with cellular electrolyte balance but with carbohydrate economy.

Morphogenic Effects

VASCULAR LESIONS. Despite the present widespread and intense interest in adrenocortical function, only few workers have directed their attention toward the morphogenic effects of adrenal corticoids on the cardiovascular system. Apart from some older observations concerning the development of endarteritis-like alterations of peripheral vessels in animals after repeated implantations of whole adrenal tissue^{137, 170, 215}, the most important observations were made by Selye and his co-workers with the experimental use of desoxycorticosterone acetate. Although this synthetic steroid is not a true representative of physiological cortical secretory activity, the results obtained with it can be interpreted with some justification as being approximately equivalent to the presumable effects of exaggerated secretion of adrenal "mineralocorticoids". Besides, one related steroid (17-hydroxy-11-deoxycorticosterone or Compound S) which occurs naturally in the adrenal cortex, was found to produce similar cardiovascular morphological changes as DCA²⁰⁵.

The vascular lesions, elicited in the rat by an over-dosage of desoxycorticosterone acetate (DCA), concern mainly the small arterics of the kidney^{137, 202, 209, 226}, of the brain²⁰² and of the splanchnic area²⁰². These lesions are quite insignificant in the otherwise untreated rat, dog, rabbit and human¹⁰², except for the brain vessels¹⁰². However, they develop in a maximal degree, resembling those in severe malignant nephrosclerosis and periarteritis nodosa, if one kidney has been previously removed and if the animals are placed on a high NaCl intake^{202, 209, 226}. Other aggravating factors are castration²⁰² and the administration of thyroxine²⁰² while certain glucocorticoids²⁰², restriction of sodium in the diet and elimination of sodium through ammonium chloride²⁰², exert a protective influence²⁰². This apparent relationship between the NaCl supply and the degree of DCA-induced vascular manifestations suggests that changes in electrolyte metabolism (intracellular sodium retention^{64, 102, 137, 225, 226}) are ultimately responsible for the DCA damage to the arterioles²⁰². In the chick, a thickening of the aortic wall and of some other large arteries was elicited by

DCA³⁰⁷¹ but gross atherosclerosis was not significantly enhanced²²²⁶. The cholesterol atheromatosis of rabbits was not intensified by injections of epinephrine-free adrenocortical extracts (cortin)²⁷²¹ in contrast to the enhancing effect of epinephrine-containing cortical lipid extracts²⁶⁶⁴ (p. 16). Neither could it be prevented by adrenalectomy^{1727, 2721}, which seems to militate against a major role of adrenal corticoids in the pathogenic mechanism of the cholesterol atheromatosis of the large vessels. Hypophysectomy was found capable of bringing DCA-induced renal vascular lesions to partial regression^{1232b}.

CARDIAC LESIONS. In otherwise untreated rats^{2692, 479, 1021}, rabbits and dogs¹⁰², DCA did not produce any significant changes in the size and weight of the heart, but in animals which were forced to exercise²³¹⁹, in chicks^{3071, 3228, 3228a} and in humans²⁶⁶⁹, a marked enlargement, especially of the left ventricle, was observed after treatment with DCA. Structural degenerative lesions, round cell infiltrations, edema and necroses were also produced by DCA in chicks³⁰⁷⁹ and rats⁴⁶⁶. They could be prevented by the intake of potassium chloride⁶⁸⁶, while addition of sodium chloride to the diet and unilateral nephrectomy seem to enhance greatly both the cardiac hypertrophy and the degenerative changes which result from DCA administration^{3056, 3091}. Low atmospheric pressure proved to be another factor, aggravating the heart-damaging effect of DCA⁴⁶⁷, which is, in part, specifically aimed at the myocardial fibroblasts⁴⁹¹. The DCA-induced cardiac hypertrophy was found to be antagonized by adrenal cortical extracts,^{1078, 2649} but not by cortisone^{1075a}. Adrenalectomy²⁶⁹² is followed by a reduction in heart size, and the cardiac hypertrophy, which normally results from unilateral nephrectomy plus ligation of the contralateral kidney, was found diminished by adrenalectomy²⁷⁴⁷. On the other hand, it was not possible to diminish the cardiac atrophy, which occurs after hypophysectomy, through the administration of adrenal cortical extracts and adrenocorticotrophic hormone^{254b}. From this it was concluded that the cardiac atrophy after hypophysectomy is not essentially caused by a secondary adrenal hypofunction^{254b}.

In view of the fact that cholesterol is considered the mother substance of adrenal corticoids²⁰⁹², it may be justified to think of the cardiac hypertrophy and fibrosis, which can be elicited in rabbits by cholesterol feeding^{1605, 1715}, as the result of an increased adrenocortical secretion.

SUMMARY. Morphological vascular changes which are induced by DCA and possibly by other mineralocorticoids, consist chiefly of arteritis-like alterations of the small vessels of the kidneys, brain and splanchnic area. They are accompanied by hypertrophy of the heart and degenerative

lesions in the myocardium. All these manifestations are markedly enhanced by an excess intake of sodium and prevented by sodium deficiency, apparently in keeping with the specific ability of DCA to deposit sodium intracellularly in muscle tissue.

The adrenal corticoids do not seem to participate significantly in the mechanism which leads to atheromatous and necrotic lesions of the large vessels, whose walls contain only few muscular elements and are more susceptible to the injurious influences of the adrenergic amines.

No reports concerning possible angio- and cardiotoxic effects of chemically identified natural corticoids have yet come to the attention of the writer.

Thyroid Hormone

Whenever reference will be made in the following to the "thyroid hormone", this should be understood as meaning either thyroxin, thyroglobulin or crude thyroid extract, unless specified, since the cardiovascular effects of the above named substances are essentially identical

Functional Effects

HEMODYNAMIC EFFECTS. Only few experimental observations on record are concerned with the peripheral hemodynamic effects produced by excess amounts of the thyroid hormone. They reveal a certain degree of elevation of the systolic pressure, while the diastolic pressure remained unchanged^{2109, 2427, 2745}, indicating an augmented pulse pressure. Only with very large doses of thyroxin was it possible to produce a marked hypertension²⁰⁹⁰. The cardiac output rises^{1863, 2463, 2745} and the stroke volume is particularly increased when cardiac action is not fast, while it may be considerably diminished during paroxysms of tachycardia²⁷⁴⁵. On the other hand, the cardiac output appeared decreased in thyroidectomized animals^{236 1966 3546} and humans⁴¹

In some instances, the pressor effect of epinephrine was found increased after thyroid administration^{2110 2930, 3215} and decreased after thyroidectomy^{1413, 2503 3009 3063}. The epinephrine sensitivity of denervated vessels was reduced in thyroidectomized dogs³⁰⁶³, and the pressor action of epinephrine was shown to depend largely on thyroid secretion^{1995 2503}. The pressor action of nor-epinephrine, angiotonin and renin was likewise diminished after thyroid inactivation²⁵⁰³. Nevertheless, thyroidectomy did not produce any marked depressor effect in animals with neurogenic and renal hypertension^{2125a}. Thyroxin was found to markedly prolong the duration of the constrictor effect of epinephrine on isolated vessels^{3157a}, possibly because of a diminution of epinephrine- and nor-epinephrine-destroying amine oxidase^{291a} in the vascular walls^{410a, 411a} under the influence of the thyroid hormone^{410a}

CARDIAC EFFECTS The most conspicuous thyroid-induced cardiac phenomena are the acceleration (frequently paroxysmic)^{2132, 2745} and intensification of the heart beat^{1913 2745 2902}, which develop within about 12 to 24 hours^{2225, 2745} following the administration of thyroid hormone and

may terminate in cardiac failure²¹⁵. By contrast, bradycardia occurs after thyroidectomy^{215a, 236, 251}.

The thyrogenic increase of cardiac action does not make its appearance in strict parallelism with the augmentation of general metabolism^{194, 243} and was therefore interpreted as the result of a direct influence of the thyroid hormone upon the heart, rather than as a secondary teleologic "adjustment" to somatic circulatory "needs"^{194, 215}.

The oxygen consumption of the heart muscle itself was found greatly increased under thyroid medication^{131, 742, 1261, 206, 247}. Thyroidectomy produces the opposite effect²⁵⁴. Myocardial glycogen stores^{37, 54, 705, 977, 1523, 2051}, creatin phosphoric acid^{125, 424, 1113} and adenosinetriphosphoric acid^{227, 1051} are depleted by the thyroid hormone. Some investigators found lactic acid in excess in the heart muscle under the influence of thyroid hormone³⁵, while others²²⁴ disagree on this point.

The dynamic and metabolic effects of the thyroid hormone upon the myocardium are accompanied by electrocardiographic changes, which consist at first of a general increase of voltage (lit, see ¹⁹⁰), but with increasing toxicity the amplitude of the T wave decreases, and frank inversion of T without or with depression of the S-T segment is not infrequently seen (lit, see ¹⁹⁰, also ^{742, 1445, 2745}). Thyroidectomy, on the contrary, is followed by a decrease of voltage^{306, 345, 346}, which is probably due to a short-circuit effect of the myxedematous body tissues and to the development of pericardial effusion¹⁹⁰. Occasionally the T wave appears inverted (lit, see ¹⁹⁰, also ^{216, 346}), possibly as a result of poor oxygen uptake by the heart muscle because of its "myxedematous" condition, in which pericapillary edema fluid separates the myocardial cells from their supplying capillaries. Administration of thyroid hormone restores the normal appearance of the electrocardiogram (lit, see ^{190, 236}).

Particular physiological and potentially pathogenic significance is to be attributed to the generally recognized phenomenon of a markedly increased epinephrine sensitivity of the heart under the influence of the thyroid hormone. It intensifies the effect of epinephrine upon heart rate, vigor of contraction, tendency toward arrhythmias^{37, 1542, 2110, 2122, 2127, 2913, 2970, 2951, 2106, 2659} (further lit, see ²⁶⁷⁸), oxygen consumption²¹²², intermediary metabolic alterations³⁰⁵¹ and cardiac death^{1549, 2532a, b, 2672} (Fig 10). On the other hand, operative removal or functional inactivation (thiouracil) of the thyroid gland diminishes the dynamic and electrocardiographic cardiac reactions to epinephrine^{290, 1542, 2679, 2951, 2997, 2100}. It also prevents cardiac death from toxic epinephrine doses even in the presence of otherwise fatal concentrations of epinephrine in the heart muscle²⁶⁷⁸. Whether the less marked potentiation of the toxicity of injected nor-epinephrine by the thyroid hormone, compared with that of epinephrine¹⁰⁴⁹, applies also to

nor-epinephrine which is directly discharged into the myocardium at the sympathetic terminals, cannot be decided at this time.

The finer mechanism through which the thyroid hormone potentiates the sympathomimetic actions upon the heart is still obscure, but recent observations by Burn^{410a} and his co-workers^{291a, 411a, 3213b} make it probable that a thyroid hormone-elicited diminution of tissue amine oxidase inhibits the local enzymatic destruction of both epinephrine and nor-epinephrine. Clinical and experimental observations suggest that even the tachycardia and other cardiac metabolic and electrocardiographic manifestations, which are induced by thyroid overfunction or hormone administration, might be essentially due to an activation or retarded inactivation of the intrinsic

**Lowest fatal myocardial concentration of epinephrine
and related compounds following injection of 2.5g/gm of epinephrine**

1928 cu./gm. [REDACTED]	Controls	(Mortality: 13% of 16 rats)
933 cu./gm. [REDACTED]	Thyroxin pretreated	(Mortality: 81% of 15 rats)

**Highest tolerated myocardial concentration of epinephrine
and related compounds following injection of 5.0g/gm of epinephrine**

1656 cu./gm. [REDACTED]	Controls	(Mortality: 43% of 15 rats)
3111 cu./gm. [REDACTED]	Thiouracil pretreated	(Mortality: 7% of 14 rats)

FIG 10 Cardiac tolerance for epinephrine markedly diminished by thyroxin and markedly augmented by thyroid inactivation (thiouracil). Average myocardial catecholamine concentrations after epinephrine injection (see also Figs 1, 2), expressed in color units per gram, each color unit equaling the color intensity of 0.001 gamma of epinephrine (After W. Raab, J. Pharmacol. & Exper. Therap. 82: 330, 1944)

amounts of cardiac sympathin (neurogenic nor-epinephrine and epinephrine from the adrenal medulla) which are normally present in the heart muscle^{682, 710, 3639}. All of the thyroid-induced rhythmic, dynamic and metabolic cardiac manifestations are qualitatively identical with those elicited by epinephrine (p. 9, 11ff.) The fact that the denervated²¹³¹ and isolated heart of thyrotoxic animals continues to beat at an accelerated rate^{2007, 2641, 3659, 3690}, is not incompatible with the above mentioned assumption for the following reasons: (a) the heart muscle possesses an outstanding tendency to accumulate and to retain sympathomimetic amines for considerable periods of time^{2678, 2672}; (b) it seems to elaborate at least a part of its own supply of sympathomimetic amines by means of embedded adrenergic tissue^{419, 1341, 3422, 3610}, even after total sympathectomy and adrenal inactivation²⁷¹¹. As regards the apparent intensification of the metabolic hypoxia-producing effect of epinephrine upon the heart muscle, it is interesting to note that

the calorogenic action of epinephrine was found weakened or lacking in thyroidectomized animals¹³⁰⁻¹³² but could be restored by thyroid feeding^{130, 131, 134}. Conversely, sympathectomized animals proved extraordinarily resistant toward thyroxine¹⁴¹. The effect of thyroxine on general oxidations could be inhibited by sympatholytic drugs¹⁴² and sympathetic denervation¹⁴³.

In contradiction to earlier beliefs, there is no definite evidence in favor of a stimulation of epinephrine secretion from the adrenal medulla through thyroxine^{134, 135, 137, 138}. It was shown, however, that acetylcholine, which is the physiological stimulant for adrenergic neurosecretion^{135, 136, 139} and which normally liberates an epinephrine-like substance (epinephrine?) from the heart muscle, does so in an exaggerated degree under the influence of the thyroid hormone and in a diminished degree after thyroidectomy¹⁴⁴. The possibility of molecular alterations of the catecholamines by the thyroid hormone is suggested by the comparison of their chemical and pharmacodynamic properties¹⁴⁵ but no major alterations of the nor-epinephrine-epinephrine ratio were seen in either thyroxine-treated or thyroidectomized animals¹⁴⁶.

The effectiveness of stimulation of the cardiac vagus is reduced by the thyroid hormone^{132, 147, 148} and increased through thyroidectomy¹⁴⁹, but the sensitivity for injected acetylcholine, which elicits a dual "amphotropic" effect¹⁴⁷ by simultaneously stimulating the vagus and adrenergic neurosecretion, was found augmented in thyrotoxic animals¹⁴⁹.

Whether and in which way the adrenal cortical atrophy which follows inactivation of the thyroid gland (exerion, thiouracil)¹⁴⁹, plays a part in the concomitant cardiovascular phenomena, is an open question. It seems still highly significant, however, that the thyroid hormone is unable to exert its augmenting effect upon oxygen consumption in the absence of the adrenal cortex and that this ability is restored through the administration of cortical extracts¹⁴⁹. Although this was only stated concerning total metabolism, it suggests the probability that the increase of cardiac oxygen consumption under the influence of the thyroid hormone may also be dependent on the integrity of adrenal cortical function in conjunction with the adreno-sympathogenic catecholamines.

SUMMARY The peripheral hemodynamic effects of the thyroid hormone are of minor significance, its cardiac action consists of tachycardia, increased stroke volume, increased myocardial oxygen consumption and loss of myocardial glycogen. It markedly sensitizes the heart to the physiological and toxic effects of epinephrine and of sympathetic stimulation (nor-epinephrine). Thyroid inactivation reverses the situation. These facts and the striking analogies between the functional and metabolic cardiac

effects of the thyroid hormone on one hand, and of the sympathomimetic catecholamines on the other, suggest that the thyroid hormone influences the heart by mediation of these amines. Besides, there are indications that the action of the thyroid hormone upon the myocardium also depends on the functional integrity of the adrenal cortex.

Morphogenic Effects

VASCULAR LESIONS. The role of the thyroid hormone in the development of lesions of the larger arteries is a rather complex one in that its toxic effects upon the media and the intima work to some extent in opposite directions, while the media *per se* seems to respond to both an excess and a deficiency of the thyroid hormone with similar morphological changes.

As far as the media is concerned, the experimental administration of large doses of thyroid hormone leads to necrotizing and calcifying lesions of the media of the aorta, the coronary arteries and other large vessels^{127, 945, 1066, 1415, 1659, 1700, 2303}, very much like those induced by epinephrine (p. 15ff.). This is not surprising in view of the well-known potentiation of the cardiovascular dynamic and metabolic²¹²² effects of epinephrine through the thyroid hormone (p. 34ff.). Accordingly, the oxygen consumption of the aortas of thyroid-treated rats was found significantly increased^{2147, 1773a}. Some thickening of the intima, which occasionally accompanies thyroid-induced media necrosis¹²⁷, is paralleled by analogous findings in epinephrine sclerosis (p. 15). The DCA-induced nephrosclerosis is intensified by thyroxin¹⁰⁹¹ and large doses of thyroxin, administered to salt-fed, unilaterally nephrectomized rats, produce a nephrosclerosis of the "malignant" type by themselves³⁰⁹⁰.

In striking contrast to its potentially injurious influence upon the arterial media, the thyroid hormone exerts a definitely protective effect against the experimentally produced deposition of cholesterol in the intima of animals^{647a, 1066, 1570, 2205, 2402, 2103, 2266b, 2411, 2712}. This was originally explained on the grounds of the hypercholesterolemia-depressing action of the thyroid hormone^{1066, 2266b, 2411}. Such a reasoning seemed sound enough until the concept of a simple, direct causal relationship between total blood cholesterol level and the development of intima lipoidosis lost much of its probability. It is becoming increasingly apparent that hypercholesterolemia *per se* (alimentary or otherwise) is not sufficient to produce atheromatosis of the arteries^{1165, 1165, 1296, 2235}, unless some other still problematic factor creates first a predisposition of the vascular wall to permit precipitation of the cholesterol¹⁴⁹⁶. Its linkage with other lipids^{675, 1633, 1735, 2511, 2620} and proteins^{1165, 2009, 2624} seems to be of great importance for the process of intravascular cholesterol deposition. Whether and in which way hormones

interfere in these subtle reactions within the blood stream, is not yet known. Thus, while hypercholesterolemia is undoubtedly a condition which favors the formation of experimental cholesterol atheromatosis, it cannot be considered the sole and decisive factor, and the atheromatois-preventing effect of the thyroid hormone can hardly be explained by its anticholesterolemic action alone. In this connection, it is of interest to note that the thyroid hormone, while inhibiting the experimentally induced cholesterol atherosclerosis, does not alter the incidence of spontaneous atherosclerosis in the chick¹²²³.

Morphological vascular changes, occurring after removal or thiouracil-inactivation of the thyroid gland, consist of two main features, namely: (a) an early developing lipoidosis of the intima^{1224, 1102, 1225}, which, however, requires very high blood cholesterol levels to become manifest¹²²⁶, and (b) hyalinization and subsequent calcification of the media^{1227, 1228}. Ultimately there results a picture which resembles closely the pattern of human arteriosclerosis^{147, 1505, 1229} and which includes the coronary and cerebral arteries^{148, 1230}.

The media lesions in hypothyroidism can certainly not be interpreted in terms of intensified local adreno-sympathogenic hypoxia, like those produced by thyroid overdosage. It may perhaps be permissible to speculate that similar alterations in tissue metabolism and structure could arise from both hypoxia due to excessive oxygen consumption and a different type of "hypoxia" caused by an inability to utilize oxygen. A lowered oxygen consumption of the aortas of rats was observed after treatment with thiouracil¹⁴⁷.

The blood cholesterol-depressing action and the protective effect of

the injurious action of large thyroid doses on the media can likewise be imitated by subcutaneous injection of potassium iodide according to some observers¹³⁰². Thus, the conclusion appears to be that the

of an potassium iodide does not take place in thyroidectomized animals¹³⁰²

CARDIAC LESIONS The most conspicuous and most regularly occurring cardiac structural change under the influence of experimentally administered thyroid hormone is myocardial hypertrophy^{107, 499, 1209, 1101, 1407, 1107, 1100} (further lit., ¹²⁰⁹), which depends more on the dosage than on the duration of thyroid medication^{1101, 1202} and can reach very marked degrees. Dilatation

of the heart was also observed¹⁴⁰⁷. With prolonged treatment, a gradually increasing tolerance for the thyroid effect seems to develop¹³⁰¹. The cardiac hypertrophy-producing actions of epinephrine and of DCA are accentuated by simultaneous administration of thyroid hormone^{1301, 3091}.

Histological findings in the myocardium of thyroid-treated animals are less uniform, largely in accordance with the dosages applied. While some workers^{160, 1225, 1145, 2132, 2729} did not find any significant microscopic lesions, others^{160, 876, 951, 1301, 1307, 1115, 3332, 3171, 3700, 3701} described cellular infiltration, hypertrophy of the muscle fibers, degeneration, edema and fibrosis, which again have much in common with the changes elicited by epinephrine (p. 18). The epinephrine-induced augmentation of myocardial oxygen consumption was found enormously increased under the influence of the thyroid hormone²¹³³, indeed, far beyond the intensification of the dynamic effects of epinephrine^{1301, 3147}. The thyroid hormone also aggravates the degenerative myocardial alterations which are elicited by DCA³⁰⁹¹.

Little experimental work has been done concerning the behavior of myocardial structure following thyroidectomy. A certain degree of cardiac atrophy^{255, 1560} was interpreted as being due to a secondary deficiency of pituitary growth hormone and to a decreased responsiveness of the heart muscle to this latter hormone²⁵⁵. In some instances, areas of hyaline degeneration, pyknotic nuclei and irregular staining were seen¹³⁰¹. More extensive observations of an analogous nature were made in human myxedematous hearts (p. 157).

Iodine compounds, administered in excess, seem to be capable of producing similar myocardial lesions as the thyroid hormone^{1407, 3342}. Marked cardiac hypertrophy and severe myocardial changes, ending in death, were elicited by small doses of iodine in rabbits with cabbage goiter¹³⁰¹.

The water content and the concentration of sodium and potassium in hearts with thyroxin-induced hypertrophy did not show any significant deviations from normal²¹⁵⁴.

SUMMARY. An over-dosage of the thyroid hormone elicits necrotizing lesions of the media of the larger vessels, which resemble those produced by epinephrine and are possibly due to the potentiation of the local hypoxiating effects of the adrenergic neurohormones. On the other hand, the thyroid hormone protects the vascular intima against the abnormal deposition of cholesterol, partly because of its blood cholesterol-depressing action.

The heart usually responds to thyroid over-dosage with marked hypertrophy and not quite so regularly with degenerative lesions, analogous to those produced by epinephrine. The injurious effects of epinephrine and of desoxycorticosterone acetate upon the myocardium are intensified by the thyroid hormone.

Lack of thyroid hormone favors the formation of intima lipoidosis and is also associated with degenerative lesions of the media and of the myocardium.

Iodine compounds in excess mimic to some extent the cardiovascular structural effects of the thyroid hormone.

Pituitary Hormones

Functional Effects

Posterior Lobe

The hormones which can be extracted from the posterior lobe of the pituitary, among them the vasopressor principle "vasopressin", originate probably in the neurosecretory cells of the hypothalamus and are stored in the pars nervosa of the pituitary^{13, 705b}.

Due to the early recognition and relatively easy demonstrability of cardiovascular effects, produced by hormonal extracts from the posterior pituitary lobe, a voluminous literature on this subject has developed over the past five decades. Countless workers have accumulated a mass of details concerning the action of posterior lobe extracts on the cardiovascular system, which seems to be somewhat out of proportion to the physiological and possible pathological significance of this hormonal material. Apart from the fact that much of the older work can be disregarded as inconclusive because of the impurity of the extracts used, the doses of the purified vasopressor posterior pituitary principle which were employed in the experimental studies of its cardiovascular effects were largely of a magnitude far beyond the amounts which can be reasonably assumed to circulate in the blood and ever to reach the vascular walls or the heart muscle spontaneously. The quantity of pitressin, produced by the posterior lobe, is relatively small, and the barrier which separates the blood stream from the cerebro-spinal fluid, into which pitressin seems to migrate through the infundibulum^{63, 711}, was found to offer considerable resistance against its penetration into the general circulation¹⁴⁸¹.

Furthermore, experimental removal of the posterior lobe proved to remain without functional consequences in the cardiovascular domain^{177 2469}. Electric stimulation of the pituitary stalk⁹⁶⁷ and of the posterior lobe itself¹³⁷⁸ causes only slight and insignificant elevations of the blood pressure¹³⁷⁸. Even the phenomenon of an intense peripheral vasoconstriction, following intracisternal injection of the vasopressor principle of the posterior lobe^{350 1451 3443}, which suggests a directly stimulating and sensitizing influence of pitressin upon medullary vasoconstrictor centers, has to be considered as a possible artefact³⁵⁰ without physiological analogy. Injection into the third ventricle, where pitressin appears naturally in highest concentrations, does not elicit an appreciable vasopressor reaction³⁴⁴³, and in humans no increase of central vasomotor irritability could be elicited through injected pitressin²⁶⁹⁴.

The presence in the cerebrospinal fluid of pressor material, believed to be pitressin, was demonstrated by several investigators^{244, 245, 246, 247, 248, 249}. However, in view of the fact that the cerebrospinal fluid contains also a vasopressor substance which is different from pitressin²⁴⁹ and more probably identical with "encephalin", a sympathomimetic pressor amine, which originates in all parts of the brain²⁴⁵, it may become necessary to revise the customary interpretation of the vasopressor property of the cerebrospinal fluid. Accordingly, the pressor effects of electrical^{250, 251, 252, 253} and chemical²⁴⁵ stimulation of the hypothalamus cannot be attributed without reservation to discharges of pitressin²⁵⁰. The undiminished occurrence of such diencephalic pressor reactions after hypophysectomy militates also against their pituitary origin²⁴⁵ and makes it appear more likely that they are elicited by neural conveyance through the sympathico-adrenal medullary system without or with involvement of the action of encephalin, the physiological role of which still remains to be elucidated²⁴⁵.

HEMODYNAMIC EFFECTS OF POSTERIOR LOBE HORMONES While pitressin (vasopressin, the pressor principle of the posterior lobe) derives its name from its prevalingly vasoconstrictor effect (older lit., see ²¹²), which was demonstrated by intracisternal^{250, 251} as well as subcutaneous injection and on isolated vessels^{252, 253}, its administration in larger doses can lead to an initial or even exclusive deep fall of the blood pressure^{254, 255, 256, 257, 258, 259}. The latter phenomenon was attributed to the admixture of histamine-like impurities²⁵⁹ or of the oxytocic posterior lobe principle which possesses depressor properties^{260, 261, 262}. Other workers^{256, 257} ascribe it to a state of myocardial weakness, brought about by spastic coronary constriction, which constitutes one of the characteristic side effects of pitressin (see below). The abolition of the pitressin-induced fall of blood pressure through epinephrine was accordingly interpreted as being made possible by an antagonistic coronary dilatation under the influence of the latter²⁵⁸ but the pressor effect of epinephrine itself was found to be intensified by posterior lobe stimulation^{262a}. Injections of large doses of pitressin in rapid succession diminish its pressor efficiency^{263, 264}, but the production of persistent hypertension in rats through repeated administration of pitressin has been reported²⁷¹. It seems noteworthy that the pressor action of pitressin in human subjects was found to be much weaker than in animals, in fact, almost negligible^{245, 272, 273, 274}, although surface capillary constriction and facial pallor are conspicuous features.

CARDIAC EFFECTS OF POSTERIOR LOBE HORMONES. The retardation of the heart beat, which usually follows the administration of pitressin^{260, 261, 275, 276, 277}, seems to be elicited by a vagal reflex, provoked by the blood pressure rise, since it can be abolished by section of the vagus²⁸⁰.

The most regular and conspicuous effect of pitressin on the heart consists of a marked constriction of the coronary arteries^{224, 731, 901, 1152, 1111, 1254, 2781}. It was even seen to result in acute death^{230, 2571}. Attempts to produce experimental congestive heart failure through prolonged infusion of posterior pituitary extract were unsuccessful²⁴¹, however.

The electrocardiogram, taken after administration of pitressin, shows, apart from an occasional increase of the P-R interval²⁷⁸¹, changes of the T-wave which vary between flattening or inversion^{751, 1115, 1152, 2299, 2751} and a distinct elevation^{751, 1307, 2299, 2613, 2781}. The T-wave-depressing effect was interpreted as being caused by myocardial anoxia due to the coronary constriction^{1152, 2299}, whereas the occasionally occurring increase in amplitude of the T-wave was explained as being provoked by antagonistically interfering vagal reflexes, elicited by the rise of blood pressure²⁶¹³. Human subjects are apparently much less prone than animals to respond to pitressin with electrocardiographic manifestations^{1290, 1305}. Premature contractions and other arrhythmias which are sometimes elicited by pitressin can be increased by the administration of thyroid hormone¹³⁰⁵.

Changes of the cardiac output under the influence of posterior lobe extract are irregular (lit., see ²⁴²¹), and denervation of the neurohypophysis was found to leave the cardiac output unaffected²⁵⁴⁶.

Pitocin, the oxytocic principle of the posterior lobe, counteracts the cardiac effects of pitressin²²⁹⁷ and slightly dilates the coronary arteries of the perfused rabbit heart³⁶⁵⁴, but seems to weaken the cardiac contractions³⁶⁵⁵.

SUMMARY. The characteristic pharmacodynamic effects of injected pitressin consist of general vasoconstriction, including the coronary arteries, with myocardial hypoxia as a result. However, these reactions are of doubtful physiological and pathogenic significance since they are produced by administration of pitressin via non-physiological routes into the blood circulation, which has not been proven to contain pharmacodynamically effective amounts of pitressin under natural circumstances. The human vascular system is largely non-responsive to injected pitressin, except for surface capillary and coronary contraction.

Pitocin possesses moderate vasodepressor properties and seems to counteract the coronary constrictor effect of pitressin.

Anterior Lobe

The influences exerted by the hormones of the anterior pituitary lobe upon the cardiovascular system, although slow, indirect and difficult to analyze, are undoubtedly of greater physiological and pathogenic im-

portance than the acute artificial effects produced by posterior lobe preparations

Among the glandotropic anterior lobe hormones, the adrenocorticotrophic hormone (ACTH) stands out as the regulator of adrenal corticoid secretion and as the king-pin substance in the endocrine mechanism of the stress phenomena and their pathogenic implications^{284 285}.

The opinions are still divided regarding the question as to whether a discharge of epinephrine is the necessary first step in the sequence of events, leading to secretion of ACTH and to the resulting stimulation of the adrenal cortex²⁹², or whether any stress-induced depletion of adrenal corticoids, the physiological inhibitors of ACTH secretion, suffices to activate the process of ACTH discharge²⁸⁴.

It has been shown that the pituitary gland does respond to local application of epinephrine²¹¹, which indicates that this substance can act upon it directly and not only as an unspecific stress-producing agent. This finding does not rule out the possible validity of the conception that a general loss of corticoids may likewise contribute to the release of ACTH. Recent observations⁶⁷⁶ seem to prove that this latter factor is at least not the only one responsible

Integrity of the anatomical connection of the pituitary with the central nervous system is no prerequisite of its response to epinephrine^{211 1021}. While this seems to eliminate the diencephalon as a necessary relay station between epinephrine action and ACTH secretion, it still leaves the possibility that physiological stimuli (neural or neurohumoral; enkephalin?) may travel from the diencephalon down into the pituitary and enhance its ACTH-secreting activity^{706 718, 1153 1254 1800, 2365} under certain conditions, e.g., emotional¹⁰²² and other stresses²³¹².

As stated before, the stimulating effect of nor-epinephrine upon the anterior pituitary is much weaker than that exerted by epinephrine^{1448, 1602 1812 2137 2415 2542}.

HEMODYNAMIC EFFECTS OF ANTERIOR LOBE HORMONES Some older experiments, which were carried out with crude anterior lobe extracts (lit., see ²⁴⁹⁵), can be disregarded because they were not conclusive on account of impurities. The hypertensive effects observed by - - -

Even the effects of the pure adrenocorticotrophic hormone ACTH must be considered with due regard to the fact that this hormone seems to provoke the elaboration and secretion of both mineralo- and glucocorticoids⁵⁷² and that the latter are capable, to some extent, of counteracting

the sodium-retaining and pressor action of the former. This may also serve as an explanation of the conflicting results which were recorded by various workers concerning the effect of ACTH on sodium metabolism^{1020, 1628, 2652}. The observation that ACTH can diminish the DCA-induced hypernatremia²⁶⁵² seems significant in this connection.

Blood pressure effects of ACTH were studied prevailingly in normotensive human subjects and proved to be either lacking or to consist only of a slight elevation of the systolic pressure^{93, 1400, 2953, 3217, 3396}, except for a few instances of a more marked response^{738, 1459, 2663} which occurred particularly in hypertensive persons⁷³⁸. An increase of vascular tone through ACTH, which is indicated by an elevation of the blood pressure "floor" during the action of tetrathylammonium chloride (blocking of ganglia), seems to be mediated by stimulation of glucocorticoid activity⁴¹⁸ (p. 45). In unilaterally nephrectomized salt-fed rats, the growth hormone (STH) of the anterior pituitary was seen to elicit hypertension³⁰⁴¹.

What has been stated above regarding the impossibility to draw precise conclusions from the effects of polyhormonal anterior lobe extracts, applies even more to the phenomena resulting from hypophysectomy. Nevertheless, the prominent role played by the adrenal cortex and especially by the mineralocorticoids in cardiovascular physiopathology, makes it probable that both the arterial hypotension^{277, 574, 2309} and the moderate diminution of experimental renal hypertension^{574, 2300, 2309}, which were observed after hypophysectomy, are due mainly to secondary adrenocortical deficiency. This is also suggested by the observation that hypophysectomized animals display a marked decrease of muscular action potentials which is even more pronounced after adrenalectomy^{2417a}.

Hypophysectomy was found to prevent an elevation of the blood pressure through DCA and it depressed the "self-sustained post-DCA hypertension"^{1712, 2310}. ACTH was incapable of restoring the latter.

CARDIAC EFFECTS OF ANTERIOR LOBE HORMONES Only very few data have been gathered concerning the relationship of the pituitary anterior lobe and cardiac function. Again, a number of earlier inconclusive experiments with crude pituitary extracts need not be quoted here. More recently it was found^{35, 56} that hypophysectomy leads to a diminution of cardiac output and that it is possible, through the administration of anterior lobe extracts, not only to correct this deficiency in hypophysectomized animals but also to elicit an absolute increase of the cardiac output in normal animals. This latter effect was likewise observed after thyroidectomy, which seems to indicate that it is at least not entirely caused by the thyrotrophic hormonal fraction of the anterior lobe extracts used.

SUMMARY. Functional cardiovascular reactions, provoked by the ad-

ministration of extracts from the anterior pituitary lobe or by hypophysectomy, depend on the degree of secondary involvement of other pituitary-dominated endocrine glands and are in general not very marked. However, since the elaboration of adrenal hormones is profoundly affected by the adrenocorticotrophic hormone (ACTH), the arterial hypotension after hypophysectomy and an occasional hypertension, developing under ACTH administration, can be considered as being prevailingly due to a secondary deficiency or excess secretion respectively of adrenal mineralocorticoids.

Morphogenic Effects

Posterior Lobe

VASCULAR LESIONS. A small number of recorded observations regarding morphogenic effects of pituitary posterior lobe extracts upon the vascular walls, suggests the possibility to produce sclerotic lesions through repeated injections of such extracts^{221, 227}. Especially the development of aortic atheromatosis in cholesterol-fed rabbits was found to be intensified by doses which had hardly any effects if combined with a normal diet^{232, 233}. Since the prolonged administration of posterior lobe extracts was accompanied by hypertrophy of the adrenal cortex, this latter phenomenon was interpreted as the ultimate cause of the vascular changes observed²³⁴. However, the results of other experiments, which speak against a significant role of corticoids in the process of intimal cholesterol deposition (p. 48) are not consistent with this concept.

CARDIAC LESIONS. Dilatation of the heart, which was observed after injection of posterior lobe extracts, is probably due to the coronary spastic action of pitressin and to resulting myocardial weakness²³⁵. Repeated administration of posterior lobe extracts can lead to cardiac hypertrophy²³⁶.

SUMMARY. The few experimental findings which suggest a certain degree of angio-cardiotoxic potency of pituitary posterior lobe hormones, are of doubtful physiopathologic significance, as they were obtained with injected doses which are hardly comparable with natural conditions.

Anterior Lobe

VASCULAR LESIONS. In view of the proven angio-cardiotoxic effects of DCA, it seems almost a foregone conclusion that extracts of the anterior pituitary, containing the adrenocorticotrophic hormone, will produce

of crude anterior lobe preparations into unilaterally nephrectomized rats, kept on a NaCl and protein-rich diet, is followed by the development of vascular changes, analogous to the DCA-induced pattern, namely, nephrosclerosis, arteriolonecrosis and periarteritis nodosa. A high protein content of the diet or the administration of protein hydrolysates⁷⁰⁸ was found to be a necessary prerequisite for the occurrence of vascular lesions under the influence of anterior lobe preparations^{239, 776, 782, 3030}, in contrast to the independence on protein feeding of the cardiovascular effects of DCA^{2635, 3090}.

There is some dissension of opinions about Selye's appealing hypothesis¹⁶⁷³ that the cardiovascular lesions which are elicited by anterior pituitary preparations, are directly attributable to a specific stimulation of the secretion of mineralocorticoids. The fact that adrenalectomy prevented the appearance of cardiovascular changes after administration of anterior lobe preparations^{1335, 1624}, is in keeping with this hypothesis. Logical as it may seem, it is not generally accepted, however, for the following reasons: (1) Sayers²⁹⁵² expresses the view that the crude anterior preparations used by Selye did not contain any appreciable amounts of active corticotrophins; (2) ACTH does not seem to be as effective in giving rise to cardiovascular lesions as DCA or as crude anterior lobe extracts^{782, 3136}; it has even been claimed to antagonize the toxic effects of DCA^{3053, 3663}, (3) there may be some general toxicity and bacterial contamination of crude pituitary preparations^{1624, 2242, 2952}.

Renal vascular lesions, similar to those produced by DCA, were elicited by the administration of pituitary growth hormone (somatotrophin, STH), presumably by way of a sensitization to the mineralocorticoids³⁰⁵¹. This effect of the growth hormone is counteracted by cortisone in doses large enough to produce adrenocortical atrophy³⁰⁷³.

Studies of the behavior of aortic intima lipoidosis in cholesterol-fed rabbits which were treated with anterior lobe hormones, showed that corticotrophic extracts did not produce any appreciably modifying effect²⁷²¹, while thyrotrophic hormone was capable of intensifying the lipoidosis⁴⁰². This paradoxical finding was interpreted as being caused by antihormone action against the thyrotrophic hormone^{402, 563}. Without simultaneous cholesterol feeding, the thyrotrophic hormone did not produce any changes of the aorta⁴⁰².

CARDIAC LESIONS What has been said in the preceding section concerning vascular lesions under the influence of anterior pituitary hormones, applies more or less also to the development of cardiac hypertrophy and myocardial degenerative changes. Such changes were observed after administration of crude anterior lobe preparations^{1335, 3073}, but not in adrenalectomized animals¹³³⁵. Cardiac hypertrophy was markedly accentuated

by combination with thyroid hormone treatment²²¹. It could not be elicited by ACTH alone²²². Growth hormone (STH) produces cardiac hypertrophy, which was found to be further exaggerated by combining it with DCA, possibly through potentiation of the latter²⁰¹.

The hearts of hypophysectomized animals were found diminished in size²²³ and the cardiac hypertrophy which develops in animals whose aortas are artificially narrowed, fails to appear after hypophysectomy²²⁴ but can be partially restored by administration of growth hormone²²⁵.

SUMMARY. Renal vascular lesions, cardiac hypertrophy and eventual myocardial degenerative lesions were elicited by the application of crude anterior lobe extracts of the pituitary and by the pituitary growth hormone. It has been claimed that the former act upon the cardiovascular system by specifically stimulating adrenal cortical secretion, but this has been questioned in view of the relative inefficiency of purified ACTH as a cardiovascular tissue-damaging agent. Growth hormone activity seems to be a necessary prerequisite for cardiac hypertrophy. Its effect is intensified by DCA and by the thyroid hormone.

Insulin

The prominent role of insulin in muscular carbohydrate metabolism, which consists generally of an increase of sugar utilization, paralleled by storage of muscular glycogen, makes it probable that an excess or a deficiency of this hormone will not remain without repercussions in cardiovascular cellular metabolism and function. However, it should be kept in mind that information regarding the effect of insulin on carbohydrate metabolism which was obtained from the skeleton muscle, does not necessarily apply to the heart muscle¹²³⁶. Cardiac dynamic function and the electrocardiogram are within certain limits independent of the amount of myocardial glycogen stores^{1235, 1236, 3473} and of the heart's supply of glucose^{918, 3147}.

It is difficult to evaluate the part played by insulin per se in the metabolic and functional reactions of the cardiovascular system, as compared with that attributable to the interfering or even overwhelming cardiovascular effects of epinephrine discharges and sympathetic stimulation. The latter accompany the biological action of insulin as a regular reflex phenomenon^{369, 489, 1438, 1857, 1890, 2671, 2902, 3409, 3425, 3692}, for which morphological evidence could also be found in the adrenal medulla^{1539, 2619}.

The administration of insulin as well as spontaneous hyperinsulinemia elicit characteristic cardiovascular manifestations, which are very similar to those produced by injected epinephrine. This speaks in favor of at least an important participation of the sympathomimetic catecholamines in the cardiovascular reactions, which are usually observed in connection with insulin activity.

In view of the fact that insulin overdosage is accompanied by discharges of epinephrine and that epinephrine, in turn, stimulates the adrenal cortex via the anterior pituitary, it is not surprising that the administration of large doses of insulin was found to be followed by signs of cortical overactivity, such as a depletion of cholesterol⁵⁰⁰ and ascorbic acid^{1123, 2199}, an eosinopenic reaction in the circulating blood⁸¹⁹ and even adrenal hemorrhages¹⁸⁹⁹. Corticotrophins were observed in the blood of humans in increased amounts during insulin action¹⁵⁷.

A temporary increase of insulin secretion seems to take place under the influence of ingested carbohydrates^{1285, 3228} and was found to be accompanied by a secondary increase in the blood level of epinephrine-like substances^{2329, 2671}, which is also indirectly suggested by corresponding cardiovascular reactions¹²⁴⁵ (see below)

Functional Effects

HEMODYNAMIC EFFECTS. Injection of insulin is usually followed by a rise of the systolic blood pressure^{1322, 1372, 1325, 1503}, while the diastolic pressure tends to fall^{1322, 1371, 1341}. The pulse pressure, cardiac output and venous pressure are increased^{1372, 1338, 1503, 1337, 1354}, and the circulation time is diminished with a resulting increase of venous oxygen¹³⁴³. All of these phenomena are analogous to those produced by epinephrine. They were found to be absent after adrenalectomy plus denervation of the heart, while adrenalectomy alone did not abolish them¹³⁵. This seems to indicate that not only adrenal medullary secretion but also general sympathetic neuro-secretion is stimulated by insulin.

CARDIAC EFFECTS. The heart action is accelerated after injection of insulin^{179, 495, 1145, 1212, 1503, 1379, 1377}, and the coronary flow was found increased¹³⁷⁷ or may remain unchanged^{1367, 1356}. Reports on myocardial oxygen consumption under the influence of insulin are contradictory. They indicate either a diminution^{139, 1273}, which was ascribed to vagal stimulation¹³⁶³, or, on the other hand, an increase⁶¹³. Myocardial glycogen synthesis seems to be augmented by insulin¹³³, but the glycogen concentration of the heart muscle may remain within normal limits even in animals which have succumbed to fatal insulin shock¹³³⁵.

Electrocardiographic changes, seen after insulin^{133, 137, 1371, 1372, 1373, 1374, 1375, 1376, 1377, 1378, 1379, 1380, 1381, 1382, 1383, 1384, 1385, 1386, 1387, 1388, 1389, 1390, 1391, 1392, 1393, 1394, 1395, 1396, 1397, 1398, 1399, 1400, 1401, 1402, 1403, 1404, 1405, 1406, 1407, 1408, 1409, 1410, 1411, 1412, 1413, 1414, 1415, 1416, 1417, 1418, 1419, 1420, 1421, 1422, 1423, 1424, 1425, 1426, 1427, 1428, 1429, 1430, 1431, 1432, 1433, 1434, 1435, 1436, 1437, 1438, 1439, 1440, 1441, 1442, 1443, 1444, 1445, 1446, 1447, 1448, 1449, 1450, 1451, 1452, 1453, 1454, 1455, 1456, 1457, 1458, 1459, 1460, 1461, 1462, 1463, 1464, 1465, 1466, 1467, 1468, 1469, 1470, 1471, 1472, 1473, 1474, 1475, 1476, 1477, 1478, 1479, 1480, 1481, 1482, 1483, 1484, 1485, 1486, 1487, 1488, 1489, 1490, 1491, 1492, 1493, 1494, 1495, 1496, 1497, 1498, 1499, 1500, 1501, 1502, 1503, 1504, 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1515, 1516, 1517, 1518, 1519, 1520, 1521, 1522, 1523, 1524, 1525, 1526, 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2689, 2690, 2691, 2692, 2693, 2694, 2695, 2696, 2697, 2698, 2699, 2700, 2701, 2702, 2703, 2704, 2705, 2706, 2707, 2708, 2709, 2710, 2711, 2712, 2713, 2714, 2715, 2716, 2717, 2718, 2719, 2720, 2721, 2722, 2723, 2724, 2725, 2726, 2727, 2728, 2729, 2730, 2731, 2732, 2733, 2734, 2735, 2736, 2737, 2738, 2739, 2740, 2741, 2742, 2743, 2744, 2745, 2746, 2747, 2748, 2749, 2750, 2751, 2752, 2753, 2754, 2755, 2756, 2757, 2758, 2759, 2760, 2761, 2762, 2763, 2764, 2765, 2766, 2767, 2768, 2769, 2770, 2771, 2772, 2773, 2774, 2775, 2776, 2777, 2778, 2779, 2780, 2781, 2782, 2783, 2784, 2785, 2786, 2787, 2788, 2789, 2790, 2791, 2792, 2793, 2794, 2795, 2796, 2797, 2798, 2799, 2800, 2801, 2802, 2803, 2804, 2805, 2806, 2807, 2808, 2809, 2810, 2811, 2812, 2813, 2814, 2815, 2816, 2817, 2818, 2819, 2820, 2821, 2822, 2823, 2824, 2825, 2826, 2827, 2828, 2829, 2830, 2831, 2832, 2833, 2834, 2835, 2836, 2837, 2838, 2839, 2840, 2841, 2842, 2843, 2844, 2845, 2846, 2847, 2848, 2849, 2850, 2851, 2852, 2853, 2854, 2855, 2856, 2857, 2858, 2859, 2860, 2861, 2862, 2863, 2864, 2865, 2866, 2867, 2868, 2869, 2870, 2871, 2872, 2873, 2874, 2875, 2876, 2877, 2878, 2879, 2880, 2881, 2882, 2883, 2884, 2885, 2886, 2887, 2888, 2889, 2890, 2891, 2892, 2893, 2894, 2895, 2896, 2897, 2898, 2899, 2900, 2901, 2902, 2903, 2904, 2905, 2906, 2907, 2908, 2909, 2910, 2911, 2912, 2913, 2914, 2915, 2916, 2917, 2918, 2919, 2920, 2921, 2922, 2923, 2924, 2925, 2926, 2927, 2928, 2929, 2930, 2931, 2932, 2933, 2934, 2935, 2936, 2937, 2938, 2939, 2940, 2941, 2942, 2943, 2944, 2945, 2946, 2947, 2948, 2949, 2950, 2951, 2952, 2953, 2954, 2955, 2956, 2957, 2958, 2959, 2960, 2961, 2962, 2963, 2964, 2965, 2966, 2967, 2968, 2969, 2970, 2971, 2972, 2973, 2974, 2975, 2976, 2977, 2978, 2979, 2980, 2981, 2982, 2983, 2984, 2985, 2986, 2987, 2988, 2989, 2990, 2991, 2992, 2993, 2994, 2995, 2996, 2997, 2998, 2999, 3000}. It seems to be well substantiated by (a) direct evidence of adrenosympathetic neurohormonal discharges (increased blood level of epinephrine)^{1359, 1359, 1371, 1372} and increased accumulation of epinephrine-like material in the myocardium¹³⁷⁵, by (b) the qualitative identity of the electrocardiographic changes produced by epinephrine and by insulin (lit., see 1960, also 1143), and by (c) the fact that the insulin-induced alterations of the electrocardiogram can be abolished by prostigmin, obviously through parasympathetic counteraction on the heart¹³⁴³. A direct effect of insulin on the heart is not affected

Insulin

The prominent role of insulin in muscular carbohydrate metabolism, which consists generally of an increase of sugar utilization, paralleled by storage of muscular glycogen, makes it probable that an excess or a deficiency of this hormone will not remain without repercussions in cardiovascular cellular metabolism and function. However, it should be kept in mind that information regarding the effect of insulin on carbohydrate metabolism which was obtained from the skeleton muscle, does not necessarily apply to the heart muscle¹²³⁶. Cardiac dynamic function and the electrocardiogram are within certain limits independent of the amount of myocardial glycogen stores^{1235, 1236, 3473} and of the heart's supply of glucose^{918, 2147}.

It is difficult to evaluate the part played by insulin per se in the metabolic and functional reactions of the cardiovascular system, as compared with that attributable to the interfering or even overwhelming cardiovascular effects of epinephrine discharges and sympathetic stimulation. The latter accompany the biological action of insulin as a regular reflex phenomenon^{369, 469, 1439, 1937, 1890, 2671, 2932, 3409, 3423, 2693}, for which morphological evidence could also be found in the adrenal medulla^{1529, 2619}.

The administration of insulin as well as spontaneous hyperinsulinemia elicit characteristic cardiovascular manifestations, which are very similar to those produced by injected epinephrine. This speaks in favor of at least an important participation of the sympathomimetic catecholamines in the cardiovascular reactions, which are usually observed in connection with insulin activity.

In view of the fact that insulin overdosage is accompanied by discharges of epinephrine and that epinephrine, in turn, stimulates the adrenal cortex via the anterior pituitary, it is not surprising that the administration of large doses of insulin was found to be followed by signs of cortical overactivity, such as a depletion of cholesterol⁵⁰⁰ and ascorbic acid^{1124, 2399}, an eosinopenic reaction in the circulating blood⁸¹⁹ and even adrenal hemorrhages¹⁸⁸⁹. Corticotrophins were observed in the blood of humans in increased amounts during insulin action¹⁵⁷.

A temporary increase of insulin secretion seems to take place under the influence of ingested carbohydrates^{1355, 2238} and was found to be accompanied by a secondary increase in the blood level of epinephrine-like substances^{2329, 2671}, which is also indirectly suggested by corresponding cardiovascular reactions¹³⁴³ (see below).

CARDIAC LESIONS No reports concerning the histology of the heart in experimental diabetes were encountered, while there are a few dealing with its reaction to the administration of insulin. Some observers^{226 227} describe disseminated necrotic patches in the myocardium of animals treated with large doses of insulin, but these changes were not considered as necessarily specific²²⁸. Indeed, other workers failed entirely to find any such lesions either after prolonged treatment with insulin^{125 127} or following shock-producing doses²²⁹. Through the latter, a certain degree of swelling and hydropic degeneration of muscle fibers could be elicited, however²³⁰. This seemed to be a reversible reaction without lasting alterations.

The above mentioned observations make it appear unlikely that insulin per se plays a significant role as a toxic agent in the origin of cardiovascular structural damage. What little cardiac injury may develop in connection with insulin-overdosage may be attributable to secondary activation of adrenal medullary and sympathetic adrenergic neuro-secretion (p. 30), the intensity of which probably does not measure up to those experimentally administered doses of epinephrine which produce more marked and more regular cardiac structural alterations (p. 18).

SUMMARY. Data concerning experimentally induced cardiovascular lesions in connection with insulin function are scant and unimpressive. It appears that insulin per se does not exert any significant direct influence upon cardiovascular structural integrity, but some slight injurious effects may be mediated by secondary insulin-induced adrenergic discharges.

the ECG⁵⁹⁶ and because of the small glucose requirement of the heart muscle^{915, 2147}.

Elimination of insulin from the body through pancreatectomy or alloxan poisoning is followed by an augmentation of the myocardial glycogen deposits^{501, 619, 921, 996, 1236}, presumably owing to failure of the diabetic heart to oxidize carbohydrates, while it maintains its ability to oxidize lactic acid^{619, 917}. No demonstrable functional cardiac abnormalities result from this state of affairs, however^{1227, 3075}.

The question as to whether the adrenosympathetic hyperactivity which accompanies insulin action, is elicited by the insulin-induced upheaval in carbohydrate metabolism throughout the tissues and by the hypoglycemia in particular, cannot be definitely answered. Neither is there a clear-cut coincidence between the time of onset and the degree of hypoglycemia on one hand and the appearance of electrocardiographic changes on the other^{1325, 1421, 1929, 2966, 3204}, nor is it always possible to normalize promptly the electrocardiogram through ingestion or infusion of glucose and restoration of a normal blood sugar level^{1421, 3204}. Of course, the blood sugar concentration does not necessarily reflect the finer changes in tissue metabolism, and thus it still does not appear improbable that the effect of insulin on cellular carbohydrate metabolism, particularly in the diencephalon, might be the starting mechanism of the accompanying adreno-sympathetic overactivity and its cardiovascular implications.

SUMMARY. A specific pharmacodynamic effect of insulin per se on the cardiovascular system has not been definitely proven. However, its administration is regularly followed by an increased adrenomedullary-sympathetic neurosecretion which can be assumed to be the decisive factor in the origin of the characteristic cardiovascular reactions occurring after injection of insulin. They are: increase of the systolic blood pressure and pulse pressure, cardiac acceleration and electrocardiographic changes, identical with those produced by epinephrine. The adrenomedullary-sympathetic stimulation is probably initiated by the insulin-induced changes in the carbohydrate metabolism of the tissues. It stimulates, in turn, the anterior pituitary and adrenal cortex.

Morphogenic Effects

VASCULAR LESIONS Only two references to experimental vascular lesions in connection with insulin function were found in the literature by this reviewer. They concern observations which indicate that dogs, surviving pancreatectomy for several months, showed atherosclerotic lesions of the aorta and the coronary arteries^{789, 1596}. No data seem to be available regarding the influence of insulin overdosage on the vascular walls

Gonadal Steroids

Although it is well known that certain phases of sexual function and involution in the human are frequently accompanied by characteristic cardiovascular manifestations, there is little evidence of any very potent direct effects of the sexual hormones upon the cardiovascular system and most of the circulatory derangements, occurring, for instance, at the age of sexual involution, have to be evaluated with consideration of concomitant pituitary and adrenal functional changes.

Functional Effects

Testosterone

HEMODYNAMIC EFFECTS OF TESTOSTERONE. Claims to the extent that testosterone is capable of reducing blood pressure and the tonus of the vascular walls^{1973, 2227, 3257, 3494}, were contradicted by other investigators who did not find any significant effect on the blood pressure of humans^{1257, 1930} or dogs^{282, 1930, 3555}. In the rat, an elevation of the blood pressure was seen both after castration²⁴⁵⁵ and under the influence of testosterone propionates¹²⁹⁹. Experimental renal hypertension is not affected by gonadectomy¹¹⁷³. A dilating action of the male sexual hormone was observed on the smallest vessels of the brain²²⁵⁷ and of the skin, the latter especially in male human castrates, whose cutaneous vessels are abnormally narrow and excitable^{340, 2756} but could be temporarily dilated³⁴⁰ and promptly restored to a normal degree of excitability by testosterone propionate²⁷⁵⁶.

Attempts to protect rats against the development of tail gangrene, due to the vasospastic toxic action of ergotamine, by administering male hormone preparations, were described as successful in normal and castrated male animals²⁷⁵⁰, but other workers^{1853, 3272} did not confirm these results.

CARDIAC EFFECTS OF TESTOSTERONE Information regarding the effects of testosterone on the heart is scanty. The muscular capacity (potential energy) of the heart muscle was claimed to be diminished after castration and to be normalized through treatment with male sexual steroids¹⁸²². Metabolic changes in the myocardium, which occur after castration, consist of a diminution of glycogen and phosphagen. They were abolished by administration of the male hormone³⁰⁵¹, and the myocardial glycogen of normal and adrenalectomized rats was likewise increased by testosterone³⁰⁵⁰. Neither castration nor injection of testosterone propionate was found

reaction of castrated cholesterol-fed female animals, in which the atheromatosis developed unimpeded despite estradiol administration¹¹³⁶. The atheromatosis of the coronary arteries of cholesterol-fed chicks could be both prevented and brought to regression by the administration of estrogens²⁵⁴⁴.

As in castrated males, the lipoid deposition in the aortic intima of cholesterol-fed female rabbits and rats is increased after castration^{2057, 2402, 2403}.

According to some investigators²⁰⁵², the aorta of normal female rabbits is richer in cholesterol than that of males. Certain birds of both sexes respond to the administration of estrogens with hyperlipemia²²⁷⁴, while this effect is not produced by testosterone²²⁷.

In an effort to duplicate the conditions of human eclampsia, some workers^{2055, 247} constricted the kidneys or renal arteries of pregnant animals and thus produced necrotizing lesions of the renal arterioles with infarctions, but these findings cannot be interpreted as indicating a specific angiotoxic effect of sexual steroids. Indeed, stilbestrol was reported to inhibit the nephrosclerosis-producing action of DCA²⁰⁵⁹.

CARDIAC LESIONS Estrogen injections do not produce any weight changes or histologic alterations of the rat heart¹⁸²², neither was pregnancy found to be accompanied by cardiac hypertrophy^{1819, 2411} in animals.

SUMMARY The most conspicuous experimentally demonstrable relationship between gonadal function and vascular structure consists of an accentuated formation of cholesterol atheromatosis in castrated rabbits and rats and of the protective effect exerted against cholesterol atheromatosis by gonadal steroids in intact female animals. Male steroids seem to possess certain "cardiotrophic" property

SUMMARY. The experimentally produced effects of male and female gonadal steroids upon the cardiovascular system are not impressive. There is no unanimity regarding claims of a vasodepressor action of testosterone and estrogens. A dilator effect of these hormones upon the small vessels of the skin is suggested both by experimental observations and by the conspicuous narrowness of the skin vessels of castrated males. Certain other cardiovascular manifestations in castrates and in cases of hypogonadism are probably attributable to concomitant pituitary-adrenal changes

Morphogenic Effects

Testosterone

VASCULAR LESIONS. Testosterone injections, even if continued over several months, do not produce any alterations of the aortic wall or of the blood cholesterol level in male rabbits²⁰⁹². In cholesterol-fed female rabbits, they were found to inhibit both hypercholesterolemia and intima lipoidosis²⁰⁹³, while this protective effect was not observed²⁰⁹⁴ in cholesterol-fed male rabbits.

Castration per se does not give rise to any significant morphological changes on the vascular walls²⁰²⁷, but the protein composition of the aortic wall tissue shows distinct abnormalities after castration, which resemble those elicited by epinephrine²⁰²⁷. This can perhaps be assumed to contribute to the increased tendency of the aortas of castrated animals of both sexes to accumulate alimentary cholesterol in the intima^{62 2037 2402 3103} and also to develop vitamin D-induced sclerosis of the media in an intensified fashion¹⁵²³. The protective action of testosterone against cholesterol atheromatosis was found lacking after castration¹⁵⁹⁶. Whether or not the hypertrophy of the adrenal cortex, which is a common sequel of castration^{1810 1813 2976 3286}, plays any role in the exaggerated development of cholesterol atheromatosis of castrated animals, cannot be decided at this time.

CARDIAC LESIONS. A "cardiotrophic" effect of male sexual steroids (androsterone and testosterone propionate) was described in rats of both sexes¹⁸⁷². It manifested itself by a slight degree of cardiac hypertrophy without histological abnormalities, while castration, on the other hand, was accompanied by a slight diminution of the heart size¹⁸⁷².

Estrogens

VASCULAR LESIONS. Prolonged series of estradiol injections leave the aorta and the blood cholesterol level unaffected²⁰⁹², but the hyperlipemia and aortic atheromatosis of cholesterol-fed intact female rabbits could be largely prevented by the administration of estradiol²⁰⁹³, in contrast to the

Necrotic lesions of the kidneys, brain and myocardium are seen as a result either of the parathormone-induced vascular alterations¹⁵⁹⁴ or of direct toxic action of the hormone⁶⁷¹.

SUMMARY. Certain changes of cardiac rhythm and of the electrocardiogram, elicited by injections of parathormone, are probably attributable, in essence, to the accompanying hypercalcemia. Parathormone induces degenerative lesions of the media of large as well as of smaller vessels, followed by local deposition of calcium of various degrees according to dosage.

Parathyroid Hormone

Functional Effects

CARDIAC EFFECTS. There exist only very few experimental observations concerning reactions of the heart to the administration of the parathyroid hormone. Bradycardia²²³, irregular alterations of the T-wave, shifting pacemaker, sino-auricular and auriculo-ventricular block, extrasystoles and ventricular tachycardia were elicited in some instances^{224 225}. Since the general biological effects of parathormone are caused essentially by increase of the blood calcium concentration, due to the mobilization of osseous calcium stores²³, it appears legitimate to draw certain conclusions regarding the potential cardiac effects of parathormone also from observations made with the extrinsic introduction of calcium into the blood circulation. Intravenous infusion of calcium chloride^{235 236, 239} produced changes of the T-wave and of auriculo-ventricular conduction only as the calcium levels were kept within the 13-65 mg per cent range²³⁶. Higher concentrations, which went far beyond physiological possibilities, were accompanied by increasing ventricular automaticity, ending in death, either from ventricular fibrillation or from cardiac arrest. The bradycardia, which is connected with moderate hypercalcemia, was ascribed to vagal action, since it could be prevented by atropine²³⁶.

Morphogenic Effects

By mobilizing calcium from the bones²⁵, the parathyroid hormone elevates the blood calcium level and favors the deposition of calcium in the tissues of the cardiovascular system. However, a necessary prerequisite for such calcifications seems to be a preceding alteration and damage of the respective cells²⁴². Administration of massive doses of parathormone is followed within one or two days by necroses of the media²³⁶, which seems to indicate that other toxic effects beside mere hypercalcemia must have been acting upon the vascular walls⁴⁷¹. Calcium is later deposited in the necrotic vascular areas so that complete solid calcification may develop in some of the smaller arteries, while calcification of the larger vessels occurs in a more uneven, spotty distribution. With less heavy doses of parathyroid hormone, the media of the smaller vessels undergoes hyaline degeneration with thickening of the intima and less extreme degrees of calcification^{370 516}.
1535, 1564 1593, 1942, 2152 2169 Calcification of the large vessels of thyroidectomized animals seems to be aggravated by the function of the parathyroid glands²³⁶².

requirement and beyond compensation by coronary dilatation; resulting in myocardial hypoxia (largely independent of heart work and coronary flow)

Diminution of myocardial glycogen, creatinine, adenylypyrophosphoric acid, increase of lactic acid.

ECG: P increased, S-T depressed; T flattened or inverted (hypoxia?), later elevated (K^+ effect?); arrhythmias; ventricular fibrillation

Cardiac effects of epinephrine intensified by thyroid hormone.

Acceleration diminished or abolished by nitroglycerine, veratramine, not markedly affected by adrenolytic drugs.

T-wave depression diminished or abolished by nitroglycerine, diminished by some adrenolytic drugs.

Accumulation of epinephrine in heart muscle beyond a definite critical concentration fatal, unless artificial respiration or thyroid inactivated or adrenolytic drugs

Morphogenic Cardiovascular Effects

Necrosis of media; thickening of intima.

Intensification of cholesterol atheromatosis of intima

Cardiac hypertrophy.

Myocardial lesions (hyaline degeneration, fibrosis).

Myocardial lesions enhanced by thyroid hormone.

General Metabolic Action

Oxygen consumption increased.

Calorigenic effect of epinephrine decreased by thyroidectomy; restored by thyroid hormone

NOR-EPINEPHRINE

(Nor-epinephrine)

Vascular and Hemodynamic Action

Systolic and diastolic pressure increased

Coronary flow

abolished by adrenolytic drugs.

SYNOPSIS OF

Experimentally Produced Functional and Morphogenic Cardiovascular Effects of the Hormones and Neurohormones

EPINEPHRINE

Vascular and Hemodynamic Action

(Epinephrine reaches vascular cells from adrenal medulla via blood or from sympathetic fibers via direct neurosecretion.)

Systolic blood pressure increased, diastolic pressure unchanged, decreased or slightly increased (the latter by large doses).

Over-all vascular dilatation (especially in musculature).

Local vasoconstriction in skin, mucous membranes, kidneys and mesentery.

Pressor effect enhanced by DCA; slightly by thyroid hormone and posterior lobe hormone of the pituitary

Pressor effect weakened by adrenalectomy, lack of Na^+ and of K^+ , and thyroidectomy.

Pressor effect inverted by adrenolytic drugs

Local vasoconstrictor effects increased by VEM, tyrosine, hypertension.

Cardiac Action

(Epinephrine reaches heart muscle cells from adrenal medulla via blood or from sympathetic fibers via direct neurosecretion; some epinephrine also formed within heart muscle by chromaffine cells, liberated under influence of acetylcholine. Accumulates in heart muscle after injection, stimulation of sympathetic, exercise, exposure to cold, etc., possibly in modified form)

Acceleration (unless prevented by reflectory vagal interference)

Stroke volume increased.

Coronary arteries dilated and flow increased

Oxygen consumption by myocardium increased beyond work energy

MINERALOCORTICOIDS (DCA)

Vascular and Hemodynamic Action

- Systolic and diastolic pressure slowly increased.
- Circulatory volume temporarily increased during DCA administration.
- Pressor effect of DCA increased by Na^+ and by K^+ ingestion.
- Pressor effect of DCA decreased or abolished by lack of Na^+ and of K^+ .
- DCA increases pressor effect of epinephrine and nor-epinephrine.
- Epinephrine-nor-epinephrine-potentiating effect of DCA weakened or abolished by lack of Na^+ .
- Pressor effect of DCA weakened by glucocorticoids.
- Pressor effect of DCA increased after adrenalectomy (absence of antagonistic glucocorticoids).
- Prolonged overdosage of DCA followed by self-sustaining persistent hypertension.

Cardiac Action

- Intracellular Na^+ in myocardial cells increased through DCA.
- ECG, S-T depressed; T flattened or inverted.
- Inotropic effect of epinephrine on frog heart increased.

Morphogenic Cardiovascular Effects

- Periarteritis nodosa-like lesions of small vessels in kidney, brain, splanchnic area, especially in unilaterally nephrectomized, NaCl-fed animals.
- These lesions aggravated by castration, thyroid hormone, growth hormone, partly abolished by hypophysectomy.
- Cardiac hypertrophy (aggravated by Na^+ ingestion, prevented by Na^+ withdrawal or K^+ ingestion).
- Myocardial lesions (edema, round cell infiltration, necroses).

GLUCOCORTICOIDS (CORTICAL EXTRACTS)

Vascular and Hemodynamic Action

- Slight increase of blood pressure. Antagonism against DCA-induced elevation of blood pressure (?).
- Increase of vasoconstrictor effect of nor-epinephrine on splanchnic vessels.

Cardiac Action

- Augmented contractile force of frog heart.

Cardiac Action

(Nor-epinephrine reaches heart muscle cells in same ways as epinephrine, but prevailing from sympathetic fibers; forms bulk of catecholamines in myocardium.)

If discharged from cardiac nerves (as concluded from effects of stimulation of cardiac sympathetic):

Acceleration;

Stroke volume increased;

Coronary arteries dilated and flow increased;

Oxygen consumption by myocardium increased beyond work energy requirement and beyond compensation by coronary dilatation; resulting in myocardial hypoxia (largely independent of the heart work and coronary flow),

ECG: T-waves flattened or inverted; cardiac acceleration and T-wave depression diminished or abolished by nitroglycerine.

If injected and circulating (specific effects modified by reflexory vagal stimulation via pressure-receptors):

Bradycardia,

Stroke volume unchanged or only slightly increased;

ECG: T-waves elevated.

Morphogenic Cardiovascular Effects

Necrosis of media (induced by electrical stimulation of vascular walls)

Coronary sclerosis in cholesterol-fed animals, and myocardial necroses elicited by enforced exercise (probably combined nor-epinephrine-epinephrine effect)

General Metabolic Action

Oxygen consumption increased (but less markedly than by epinephrine).

SYMPATHECTOMY (WITHOUT OR WITH ADRENALECTOMY)*Vascular and Hemodynamic Action*

Blood pressure decreased

Cardiac Action

Catecholamines in heart muscle diminished

Bradycardia.

Refractoriness of heart to thyroxin action.

Morphogenic Cardiovascular Effects

Heart size decreased

ECG: voltage increased; S-T and T occasionally depressed.
 Cardiac effects of injected epinephrine increased.
 Liberation of epinephrine in heart muscle increased.
 Fatal epinephrine concentration in heart muscle decreased.

Morphogenic Cardiovascular Effects

Media necrosis and calcification in large vessels.
 Intensification of DCA-induced lesions of small vessels.
 Production of nephrosclerosis by very large doses.
 Prevention of cholesterol atheromatosis of intima (partly through diminution of hypercholesterolemia).
 Cardiac hypertrophy
 Myocardial lesions: occasionally edema, cellular infiltrations, fibrosis.
 Intensification of epinephrine- and DCA-induced cardiac lesions.

General Metabolic Action

Oxygen consumption increased (through catecholamine activation?).
 Oxygen consumption-increasing effect weakened after sympathectomy and after adrenalectomy, restored by cortical extract.
 Tissue amine oxidase diminished

THYROIDECTOMY (THIOURACIL)

Vascular and Hemodynamic Action

Circulatory velocity decreased
 Pressor effect of epinephrine and nor-epinephrine decreased.

Cardiac Action

Bradycardia

...

...

... sympathetone weakened.

Liberation of epinephrine in heart muscle weakened.
 Fatal epinephrine concentration in heart muscle increased

Morphogenic Cardiovascular Effects

Cholesterol atheromatosis of large vessels enhanced
 Hyalinization and calcification of media of larger vessels.
 Slight decrease of heart size
 Degenerative foci in myocardium (occasionally).

Morphogenic Cardiovascular Effects

Protection of small vessels against DCA-induced lesions.

ADRENALECTOMY*Vascular and Hemodynamic Action*

Blood pressure decreased.

Pressor effect of epinephrine diminished.

Decrease of renal and centrogenic hypertension.

VEM formation impaired.

Cardiac Action

Catecholamines in heart muscle slightly decreased.

Bradycardia.

ECG: low voltage, occasionally depression of S-T and T.

Morphogenic Cardiovascular Effects

Heart size decreased.

Prevention of cardiac hypertrophy, otherwise induced by crude anterior pituitary lobe extracts

General Metabolic Action

Oxygen consumption diminished

Calorigenic effect of thyroid hormone impaired, restored by cortical extracts.

THYROID HORMONE

(Cardiovascular effects of thyroid hormone probably mediated by activation of intrinsic sympathomimetic catecholamines, especially of epinephrine)

Vascular and Hemodynamic Action

Systolic blood pressure slightly increased (markedly by very large doses)

Pressor action of epinephrine and nor-epinephrine increased.

Cardiac Actions

Acceleration.

Stroke volume increased (except in case of marked tachycardia).

Myocardial oxygen consumption increased.

Myocardial glycogen, creatine-phosphoric acid, adenosine-triphosphoric acid diminished.

Morphogenic Cardiac Effects

Crude anterior lobe extracts: cardiac hypertrophy in unilaterally nephrectomized salt-fed animals, aggravated by thyroid hormone.

ACTH: no effect on heart size.

Growth hormone: cardiac hypertrophy, aggravated by DCA.

HYPOPHYSECTOMY*Vascular and Hemodynamic Action*

Blood pressure decreased

Renal hypertension decreased.

Cardiac Action

Cardiac output decreased

Heart size decreased, no cardiac hypertrophy despite ligation of aorta.

INSULIN

(Cardiovascular effects of insulin essentially due to secondary discharge of epinephrine and possibly nor-epinephrine.)

Vascular and Hemodynamic Action

Systolic pressure increased.

Diastolic pressure unchanged or decreased.

Cardiac Action

Catecholamines in heart muscle increased

Acceleration.

Coronary arteries dilated.

Myocardial glycogen increased (probably direct insulin action).

ECG: S-T depressed, T-wave flattened or inverted (probably epinephrine effect)

Morphogenic Cardiovascular Effects

Occasionally degenerative foci in myocardium.

TESTOSTERONE*Vascular and Hemodynamic Action*

Blood pressure effect contradictory

Dilatation of small vessels (brain, skin).

Morphogenic Cardiovascular Effects

Prevents cholesterol atheromatosis in female animals (not in males).
Slight cardiac hypertrophy

General Metabolic Action

Oxygen consumption decreased (through inactivation of epinephrine?).

POSTERIOR PITUITARY HORMONE (VASOPRESSIN)

(Questionable whether posterior pituitary hormone ever enters blood circulation in quantities comparable to those used in experiments.)

Vascular and Hemodynamic Action

Blood pressure increased or decreased (the latter by large doses, possibly because of coronary constriction and resulting myocardial weakness).

Over-all vasoconstriction.

Cardiac Action

Bradycardia.

Coronary constriction

ECG: T-wave depressed or inverted (hypoxia) or elevated (vagus interference?); arrhythmias.

Morphogenic Cardiovascular Effects

Aggravation of cholesterol atheromatosis of aorta.

Cardiac hypertrophy (moderate) and dilatation.

ANTERIOR PITUITARY HORMONES

(Cardiovascular effects of anterior pituitary hormones probably largely mediated by adrenocortical hormones and thyroid hormone.)

Vascular and Hemodynamic Action

ACTH: blood pressure slightly increased

Growth hormone: blood pressure increased in unilaterally nephrectomized, salt-fed animals.

Morphogenic Vascular Effects

Crude anterior lobe extracts and growth hormone: nephrosclerosis, arteriolonecrosis, periarteritis nodosa (DCA-like lesions) in unilaterally nephrectomized salt-fed animals, these lesions aggravated by high protein diet.

ACTH: similar but less pronounced lesions.

Thyrotropic hormone: intensification of cholesterol atheromatosis of intima (due to anti-hormone formation?).

Cardiac Action

Bradycardia.

T-wave changes, arrhythmias.

Morphogenic Cardiovascular Effects

Hyalinization, necrosis and calcification of media of large and small vessels

Necrotic lesions in kidneys, heart, brain.

ESTROGENS

Vascular and Hemodynamic Action

Blood pressure effect contradictory.

Dilatation of small vessels (skin).

Prevents ergotamine-epinephrine-induced tail gangrene (rat).

Cardiac Action

Myocardial glycogen increased.

Morphogenic Cardiovascular Effects

Prevents cholesterol atheromatosis in female animals (not in males)

CASTRATION

Vascular and Hemodynamic Action (in males)

Blood pressure effect contradictory.

Constriction of skin vessels.

Cardiac Action (in males)

Myocardial glycogen and phosphagen decreased

Muscular energy of heart muscle diminished

ECG: voltage decreased.

Morphogenic Cardiovascular Effects (in males)

Alteration of protein composition of vascular walls

Intensification of cholesterol atheromatosis of intima

Intensification of Vitamin D sclerosis of media

Heart size slightly decreased.

Vascular and Hemodynamic Action (in females)

Blood pressure effect contradictory.

Morphogenic Cardiovascular Effects (in females)

Alteration of protein composition of vascular walls

Intensification of cholesterol atheromatosis of intima.

No effect on heart size

PARATHYROID HORMONE

(Parathyroid hormone effects on cardiovascular system due in part to hypercalcemia, in part to a hypothetical direct toxic action and in part to secondary kidney lesions)

III

CARDIOVASCULAR FEATURES IN ENDOCRINE AND NEUROENDO- CRINE SYNDROMES

Adrenals

Adrenosympathetic Pheochromocytomas and Paragangliomas

The clinical syndrome which is caused by the presence in the human body of an adrenergic neurosecretory tumor was first described by Volhard¹²⁷⁶ in 1907, by Helly¹²⁸⁴ in 1913, and by Labbé, Tinel and Doumer¹²⁸⁸ in 1922. For many years, it was considered an extremely rare morbid condition of comparatively little practical importance because numerous cases had remained undiagnosed. In some, the acute symptoms, occurring in the absence of the attending physician, were belittled by the latter as "hysterical" or as malingering schemes because physical examination, carried out in the intervals, failed to reveal any objective criteria of disease. Others were mistaken for essential hypertension, chronic nephritis, thyrotoxicosis, migraine, paroxysmal tachycardia, coronary infarction, tabetic crises, malaria, etc. Owing to the accidental discovery of such tumors in the process of subdiaphragmatic sympathectomies, to improvements of the diagnostic technique, and to the fact that the attention of practicing physicians in general was more sharply focused upon this syndrome, the number of correctly diagnosed and successfully treated cases has rapidly increased in recent years, so that hundreds of them are on record at this time.

In the following discussion, we shall consider only those adrenal medullary tumors and neoplasms of the sympathetic nervous system which consist at least in part of proliferating mature chromaffin cells and which yield sympathomimetic catecholamines as the agents giving rise to cardiovascular clinical manifestations. Consequently, the sympathogoniomas, neuroblastomas (such as the Pepper and Hutchinson tumors), and the ganglioneuromas will be disregarded.

Endocrine Pathology

... .. automen, chest or neck, or even inside the cranium¹²⁸⁹, are referred to as paragangliomas or are also included by some in the term pheochromocytoma. For the sake of convenience, we shall adopt the latter practice in the following.

The majority of medullary pheochromocytomas originates in the right adrenal. In 9-12 per cent of the cases, tumors were found in both glands^{1290, 1291}. Their maximal dimension ranges from about one to more than 12

in the blood of abnormally large amounts of epinephrine-like material during acute hypertensive paroxysms^{290, 289, 311, 312, 313, 1615, 2201, 2100}. These increases varied in wide ranges from twice²¹⁰⁰ to five-fold²⁸⁹ and 1000-fold²²⁰¹. Normal values were encountered in the blood of pheochromocytoma cases during more or less symptom-free periods^{290, 2207, 2719, 2100}. A certain relationship between colorimetric findings and fluctuations of the blood pressure could be ascertained in one case of suspected but not verified pheochromocytoma (Fig. 37, p. 276). In the urine of pheochromocytoma patients, the presence of excessive amounts of nor-epinephrine and epinephrine has been demonstrated by means of pharmacodynamic tests^{271, 275, 282, 1101}, but in some instances, no free pressor catecholamines were found²⁵¹.

The mechanism of adrenal medullary secretion is controlled by the central and sympathetic nervous system (p. 3), probably in part by means of the changing tonus of circular muscular fibers of the adrenal veins^{2219, 2400}, which seem to act in the fashion of a valve and which can be assumed to play also a role in the clinical status of pheochromocytoma cases by holding back or releasing the hormonal products of the tumor.

Metabolic and Diencephalic Symptoms

Among the clinical manifestations of pheochromocytomas, there are several which, although not limited to the cardiovascular system, may be of significance in the interpretation of some of the cardiovascular phenomena. One of these is the frequently, though not invariably, present elevation of the basal metabolism^{164, 399, 925, 1177, 1214, 1630, 1511, 1732, 1740, 1941, 2126, 2107, 2107, 2071, 2719, 2107, 2107} which may reach excessive heights, such as plus 142 per cent²⁷¹⁹ (Fig. 11). This form of labile hypermetabolism is not caused by an increase of thyroid function, as evidenced by its refractoriness to thyroidectomy and to thiouracil compounds^{1214, 2719}, and by the absence of high blood iodine levels^{1102, 2719}. It rather seems that the intensified oxygen consumption

with epinephrine-induced calorigenic adrenal cortical over-activity^{1112, 2200, 2107}, since the symptom of hypermetabolism has been seen to disappear promptly and completely after surgical removal of the neoplasm²⁷¹⁹. In some of the cases, the BMR was not found elevated (lit., see ²⁰⁰¹) at the time when tests were taken. It is possible that the elevation of the BMR is in the presence of small tumors. Besides, one cannot rule out the possibility of temporary elevations at other times in the variable course of the pheochromocytoma syndrome. The exact mechanism by which epinephrine increases the respiratory metabolism is still problematic, despite a large amount of work devoted to

cm³¹⁸⁹. They may be solid or cystic. Approximately 12 per cent of the clinically active pheochromocytomas on record were located outside of the adrenal glands^{413, 1102, 1618}. About 9 per cent of the tumors are malignant²⁷¹. Cardiovascular symptoms are absent in some of these malignant metastasizing neoplasms²¹³⁹ and also now and then in an exceptional case of benign pheochromocytoma³²⁰⁹. Most of the tumors develop in middle-aged persons¹²⁴¹, yet no age group is entirely exempt, as pheochromocytomas have been observed in infants from the 16th month up and in individuals beyond the 60th year¹⁵⁴⁷. The distribution among both sexes is about equal^{899, 1547, 2455}.

Hormone Production and Secretion

In numerous instances of pheochromocytoma, extracts of the tumors, removed by surgery or at autopsy, revealed almost uniformly the presence of material which was originally believed to be epinephrine in consideration of its pressor and other pharmacodynamic effects and because of certain chromogenic properties (lit., see ²¹⁵⁹). More recent studies, however, made a revision of these older interpretations necessary, since it was shown that both the normal adrenal medulla (p. 3) and the chromaffin tumors contain considerable quantities of nor-epinephrine besides epinephrine. Indeed, while the nor-epinephrine content of the normal gland usually amounts to less than 30 per cent, this substance constituted from 50-90 per cent of the hormonal material, recovered from pheochromocytomatous tissue^{250, 261, 453, 1177, 1179, 1355, 1807, 2607} in 10 out of 11 cases in which the modern differential techniques of analysis were applied. Only in one case was there a preponderance of epinephrine. These findings seem to support the hypothesis^{251, 2607} that the pheochromocytoma cells are generally incapable of adequately performing the process of nor-epinephrine transformation into its methylated homologue epinephrine. The hormone content of pheochromocytomas was estimated as being increased to concentrations as high as 40 mg per gram, compared with 1-2 mg of estimated catecholamines per gram of normal medullary tissue⁸⁹⁹. There was no significant difference in the hormone content of tumors removed from patients exhibiting paroxysmal hypertension as compared with tumors from individuals with sustained hypertension¹¹⁷⁷. The blood level of inactive "adrenalinogen" was not found abnormally high during hypertensive paroxysms¹⁹⁵⁰.

... both nor-epinephrine and epinephrine without further chemical alteration in the proportion in which they are elaborated inside the tumor, but more direct information than at present available will be needed concerning this question. A number of recorded observations in verified cases of pheochromocytoma indicate the presence

in the blood of abnormally large amounts of epinephrine-like material during acute hypertensive paroxysms^{270, 269, 211, 254, 259, 1015, 2301, 2167}. These increases varied in wide ranges from twice²¹⁶⁰ to five-fold¹⁹⁹ and 1000-fold²⁰¹. Normal values were encountered in the blood of pheochromocytoma cases during more or less symptom-free periods^{240, 252, 219, 216}. A certain relationship between colorimetric findings and fluctuations of the blood pressure could be ascertained in one case of suspected but not verified pheochromocytoma (Fig. 37, p. 276). In the urine of pheochromocytoma patients, the presence of excessive amounts of nor-epinephrine and epinephrine has been demonstrated by means of pharmacodynamic tests^{211, 25, 242, 114}, but in some instances, no free pressor catecholamines were found²⁴.

The mechanism of adrenal medullary secretion is controlled by the central and sympathetic nervous system (p. 3), probably in part by means of the changing tonus of circular muscular fibers of the adrenal veins^{2114, 240} which seem to act in the fashion of a valve and which can be assumed to play also a role in the clinical status of pheochromocytoma cases by holding back or releasing the hormonal products of the tumor.

Metabolic and Diencephalic Symptoms

Among the clinical manifestations of pheochromocytomas, there are several which, although not limited to the cardiovascular system, may be of significance in the interpretation of some of the cardiovascular phenomena. One of these is the frequently, though not invariably, present elevation of the basal metabolism^{224, 209, 224, 1177, 1241, 1430, 1247, 1752, 1540, 1941, 2126, 2407, 2027, 2641, 2119, 242} which may reach excessive heights, such as plus 142 per cent²¹¹³ (Fig. 11). This form of labile hypermetabolism is not caused by an increase of thyroid function, as evidenced by its refractoriness to thyroidectomy and to thiourea compounds^{1244, 2119}, and by the absence of high blood iodine levels^{1102, 2119}. It rather seems that the intensified oxygen utilization in pheochromocytoma cases is due to the specifically oxygen consumption-stimulating, calorogenic action of the sympathomimetic neurohormones which are discharged from the chromaffin tumors (p. 74), possibly in conjunction with epinephrine-induced calorogenic adrenal cortical over-activity^{1192, 2006, 2407}, since the symptom of hypermetabolism has been seen to disappear promptly and completely after surgical removal of the neoplasm²¹¹⁹. In some of the cases, the BMR was not found elevated (lit., see ²⁶⁴⁴) at the time when tests were taken. It was suggested that this happens especially in the presence of small tumors which produce predominantly nor-epinephrine²¹⁷. Besides, one cannot rule out the possibility of temporary elevations at other times in the variable course of the pheochromocytoma syndrome. The exact mechanism by which epinephrine increases the respiratory metabolism is still problematic, despite a large amount of work devoted to

this question¹²⁷⁴. The calorigenic effectiveness of nor-epinephrine is less pronounced^{2106a}.

Hyperglycemia, although often present (lit, see ¹²¹, ²⁶⁵⁵), is not as regularly observed, even during paroxysms, as one might expect if only epineph-



FIG 11 Case of Smithwick 28 yrs rate 120-130 (after normal), BMIR +60 operation 70%¹⁷¹⁹ (see also Fig. 12)

tumor by Dr R H 10-135/72-100), heart T2 (after operation +51% in 2 hours (after

rine were discharged by the tumors. Many observers were puzzled by this apparent contradiction, but since it is now known that most pheochromocytomas produce prevalingly nor-epinephrine, the absence of hyperglycemia can be explained by the fact that the effect of nor-epinephrine upon the blood sugar level is much weaker than that of epinephrine^{1179 1359 3123}

Some cases of pheochromocytoma present symptoms such as hyperhidrosis, hyperthermia, polydipsia, polyuria, polyphagia, and amenorrhea, which suggest a functional involvement of diencephalic centers (lit, see ²⁶⁴⁴) and

the hypothetic possibility¹²² that certain chromaffin tumors may produce their neurovegetative manifestations not only through the discharge of the known sympathomimetic neurohormones, but also through some as yet unidentified nervous pathways. Recent observations make it probable that epinephrine acts as a catalyst for oxidative brain metabolism^{176a, 189a}, while nor-epinephrine is rather ineffective in this respect^{176a}. Epinephrine increases, nor-epinephrine decreases the cerebral blood flow^{176a}.

Occasionally the thyroid was found enlarged in cases of pheochromocytoma, either permanently^{205, 209, 210, 247} or by temporary swelling¹²¹. Although such observations are interesting, they do not prove a generally basic role of a disturbed thyroid function in the pathogenic mechanisms of the pheochromocytoma syndrome.

Hypertensive Paroxysms

For many years it was widely believed that paroxysmal blood pressure crises constitute the most important pathognomonic feature of the pheochromocytoma syndrome, and in their absence a chromaffin tumor was hardly ever suspected. More recent experience has made it clear, however, that numerous cases do not display any of the dramatic criteria of a "sympathetic storm" but may remain disguised for an indefinite period of time under the appearance of an ordinary essential hypertension.

While the older clinical literature on pheochromocytomas deals almost exclusively with the paroxysmal type, only about one-half of the newer case descriptions are concerned with this form of blood pressure abnormality. The paroxysms are usually accompanied by other neurogenic phenomena, such as intense headaches, coldness of the hands, profuse perspiration, fever, pallor, anxiety, tremor, paresthesias, nausea, mydriasis, and even convulsions^{124, 126}. They are often elicited by emotional excitement, muscular effort, change of position, etc., but they may also occur out of the clear sky without any recognizable reason or warning. Both the systolic and diastolic pressures may rise rapidly to extreme heights (for instance, 300/240) and oscillate in wide ranges for periods lasting a few minutes to several hours. Such severe attacks are frequently followed by a drop of the blood pressure deep below the normal level and by a state of shock-like exhaustion. In other cases, the pressure elevations more moderate, the pressure tends to fall rather than rise, probably due to an unusual prevalence of epinephrine, which is likely to lower the diastolic pressure¹²⁴. There are also cases where the blood pressure may remain normal over years.

In more advanced stages, however, the attacks occur with greater frequency

and the "resting" blood pressure climbs gradually to higher levels at which it may become stabilized very much like in essential hypertension.

Sustained Hypertension

During recent years a correct diagnosis was made of many pheochromocytomas which did not produce acute hypertensive attacks but rather a more or less slowly and insidiously developing type of arterial hypertension. Such cases showed all the characteristics of essential hypertension, including its typical renal, ophthalmic and cardiac complications (lit, see ²⁶⁹³). These similarities are not accidental. They indicate a close pathogenic relationship between the pheochromocytoma-induced neurohormonal hypertension and essential hypertension. The main difference seems to lie in the fact that in pheochromocytomatous hypertension the vasopressor material is being produced and secreted by one single compact cell group, namely the tumor, which permits its complete surgical elimination, while in genuine essential hypertension analogous vasopressor substances are probably discharged diffusely by myriads of neurosecretory sympathetic nerve endings into the vascular walls, without passing through the blood stream. It must be emphasized, however, that successful removal of the tumor is not followed without exception by a return of the blood pressure to normal levels. In such cases, the continued activity of other secondary pressor mechanisms must be assumed¹¹⁷⁷ which may also be responsible for the maintenance of high blood pressure levels in some cases of pheochromocytoma while the tumor is still *in situ* but not necessarily constantly secreting. Whether these additional mechanisms are central nervous (p 267ff.) or adrenocortical (via the pituitary-ACTH mechanism?) remains to be elucidated.

Blood Pressure Reactions and Diagnostic Tests

The reactions of the blood pressure of patients who harbor a pheochromocytoma to reflex stimuli and to certain drugs are so irregular and unpredictable that their differential diagnostic usefulness has to be regarded as a very limited one, with the exception of the response to a few drugs to be mentioned later. Even muscular exercise, which often serves as the trigger mechanism for severe hypertensive attacks (lit, see ²⁶⁹³), may be paradoxically accompanied by a fall of blood pressure²⁷¹⁹. Orthostatic hypotension usually occurs in cases with chronically elevated blood pressure^{151 257 2719 2776}, but, on the other hand, a sudden change from the recumbent into the erect position can call forth a hypertensive paroxysm⁶⁴. The response to the cold pressor test may vary between extremely exaggerated^{181 224 1814 2101 2574 347} and subnormal reactions of the blood pressure^{1347 1941 347}. Injections of epinephrine are likewise apt to elicit abnormally intense^{200 459 2719} or

abnormally weak^{153, 161, 162, 2267, 3101} effects. Hyperventilation has been seen to provoke hypertensive paroxysms which are possibly attributable to the mechanical massaging action of the diaphragm upon the tumor^{161, 154, 234}. In one case of sustained hypertension, hyperventilation was accompanied by a deep fall of both the systolic and diastolic pressures to normal levels (Fig. 12). This was interpreted as the response of over-sensitive vasomotor centers to the lowering of blood CO_2 ²⁷¹⁹. The comparative regularity with

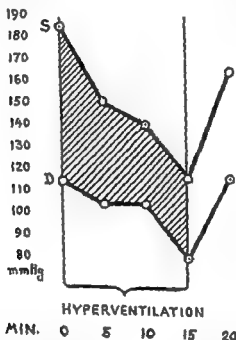


FIG. 12 Fall of blood pressure during hyperventilation in a patient with pheochromocytoma and sustained hypertension (After W. Rash and R. H. Smithwick, *J. Clin. Endocrinology* 9: 782, 1949)

which the H^+ - - - - -
biturates¹⁶⁹
which point
the presence
amine ("encephalin")²⁶⁸² is in any way involved in these reactions, cannot be decided at the present time

Among the drugs which have been used for diagnostic purposes, there are those which are capable of provoking typical attacks, such as histamine²⁷⁴, methylethylchloride¹¹¹², tetraethylammonium bromide¹⁷² and insulin¹¹⁷. They act apparently through the release of nor-epinephrine and

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is administered in "adrenolytic" doses, i.e., in amounts sufficient to block the pressor effect of circulating epinephrine but not to act in a "sympatholytic" fashion, i.e., to inactivate the sympathogenic catecholamines inside the vascular muscle cells which are probably a decisive factor in essential hypertension. Benzodioxane reverses the epinephrine effect into a fall of blood pressure, presumably by leaving its partially vasodilator action intact. The pressor effect of nor-epinephrine, which is not accompanied by a vasodilator mechanism, is weakened or abolished by benzodioxane but does not become reversed^{223, 224}

The benzodioxane test for pheochromocytoma²²⁵ is performed as follows: Into a brachial vein of the recumbent patient, who should not have taken any sedatives, isotonic saline solution is infused by slow drip through a three-way stopcock or an ordinary plastic intravenous set. As soon as the blood pressure level has become definitely stabilized and several readings at short intervals have given reasonably constant results, the calculated dose (see below) of benzodioxane is slowly injected over three minutes, either through the three-way stopcock or directly into the tubing. The blood pressure should be followed by an assistant at half-minute intervals during the injection and at one-minute intervals during the following 15 minutes or so, until the pressure has returned to its original level. The dosage is based upon the patient's body surface area, which can be readily determined from basal metabolism charts after measurement of his height and weight. Ten mg. of benzodioxane (in 1-2 per cent solution) per square meter of body surface are being used as the standard dose, which amounts to a total of 15-20 mg in average adults. Some clinicians²²⁶ simplified the procedure by giving 20 mg in all adult cases.

In the absence of a pheochromocytoma, the blood pressure will in the vast majority of cases remain unchanged during the injection or it may rise to considerable heights²²⁷. On the other hand, if the patient harbors a chromaffin tumor and if his hypertension is at least in part due to circulating epinephrine, there will be a significant depression of the blood pressure during or immediately after the injection of benzodioxane, which will persist for 8-15 minutes. This response, if present, is almost definitely pathognomonic for pheochromocytoma except in cases of uremia (p. 480). However, it has been found lacking in a number of cases of proven tumors of this kind^{228, 229, 230}. Possible reasons for these exceptions from the rule might be either an almost exclusive secretion of nor-epinephrine or a temporary secretory inactivity of the tumor at the time of the test, other mechanisms maintaining the blood pressure at an elevated level, e.g., adrenal corticoids under the influence of an over-stimulated anterior pituitary²³¹. Despite such occasional deviations, the benzodioxane test remains a very valuable diagnostic tool, especially also because its side effects

epinephrine from the tumor. Furthermore, there are those which by virtue of their adrenolytic properties cause a fall of blood pressure, such as benzo-dioxane¹¹⁸³, dibenamine hydrochloride²²¹⁰ and regitine⁵⁶⁰.

The *histamine test*, which was introduced in 1945 by Roth and Kvale²⁵⁷⁴, is the one most widely used for the diagnosis of pheochromocytomas which produce the paroxysmal type of hypertension^{459, 1430, 1941, 2401, 2574}. Rapid intravenous injection of 0.025 to 0.05 mg histamine base in 0.25 to 0.5 cc of saline solution (or the double amount, if necessary, because of dubious response) is followed by a sudden intense rise of the systolic and usually also of the diastolic blood pressure, which reaches its peak approximately at the end of the second minute and which is accompanied by the familiar neurovegetative and subjective symptoms, thus permitting a detailed evaluation of the clinical picture. Within 5-10 minutes the pressure returns to near the starting level. It is a characteristic of the histamine reaction in pheochromocytoma patients that the blood pressure rise exceeds that provoked by the cold pressor test (immersion of the lower arm in ice water for 60 seconds) in the same patient²⁵⁷⁴, while in normotensive persons and in other forms of hypertension the reaction to histamine is weaker than the cold pressor response. In the latter cases, no other side reactions occur, except headache and tachycardia. No sedatives or depressor drugs must be given before either of the two tests, as they are likely to diminish the cold pressor effect but not the histamine effect, and thus to create misleading results. It is advisable, however, to keep injectable barbiturates or adrenolytic drugs (benodaine, hydergin, regitine) in readiness in order to combat dangerously severe reactions. Some workers²²¹⁴ in whose experience both false negative histamine tests in pheochromocytoma patients and false positive tests in essential hypertension are not uncommon events, give preference to the mecholyl test (10 mg s.c.; "overshoot" over the cold pressor test within 30 minutes after injection) which they consider more reliable.

In the presence of sustained pheochromocytomatous hypertension, the provocative tests are of lesser usefulness. These are the cases which, from a practical point of view, pose the most baffling and at the same time the most fateful diagnostic problem, because their recognition means often the crucial decision between a life- and health-saving operation, especially in younger individuals, and the resignation to palliative measures of doubtful value. It was an important step forward, therefore, when Goldenberg and co-workers (1947) applied benzo-dioxane compounds which, probably by competing with epinephrine for its specific cellular receptors⁴⁵¹ and thus inactivating it, revealed that component of existing hypertension which is due to circulating epinephrine. Piperidylmethylbenzo-dioxane (933F, Benodaine), the drug which is now being generally used for this purpose,

Peripheral Circulation; Temperature; Ocular Vessels

Hypertensive paroxysms, due to pheochromocytomas, are almost invariably accompanied by constriction of the skin vessels which produce pallor and coldness of the body surface. The axillar, rectal, and oral temperatures can rise to extreme hyperpyrexia during the attacks (lit., see ²⁸³) so that a considerable discrepancy between skin and body temperature is apt to exist.²⁸⁴ After termination of the attack, the skin vessels sometimes dilate, thus giving rise to flushing and to a sensation of heat.

In cases of chronically sustained pheochromocytomatous hypertension, a significant diminution of the peripheral blood circulation and of the skin temperature has been observed together with somewhat elevated rectal temperatures.²⁸⁵ This characteristic behavior disappeared after removal of the tumor. It may be of some diagnostic significance. Prolonged slight elevations of the body temperature are frequently present. In one case, there was a several days' episode of apparently diencephalic hyperpyrexia in the absence of any paroxysmal symptoms.²⁸⁶ The same patient displayed marked acrocyanosis of the extremities which vanished after removal of the tumor.²⁸⁷

Abnormalities of the retinal vessels are particularly common in pheochromocytoma cases with permanent hypertension (lit., see ^{288 289 290}). They are of the hypertensive type without or with hemorrhages and retinopathies. Arterio-sclerotic lesions are less conspicuous. There is no strict parallelism between blood pressure level, renal involvement and retinal lesions. The latter may occur even during childhood. Removal of the tumor is not infrequently followed by partial or complete normalization of the eye grounds and vision.^{291 292 293}

Kidney Function

Slight to moderate albuminuria, abnormal sediments and other signs of intermittent or permanent renal damage²⁹⁴ appear in many pheochromocytoma patients already at an early stage of the disease, especially in those with chronic hypertension, but also during and immediately after hypertensive paroxysms.^{295 296 297 298} Signs of renal insufficiency, such as subnormal phenol-sulphonphthalein excretion and azotemia, may be present but only a small minority of cases.²⁹⁹

In some instances

no renal functional impairment³⁰⁰ is demonstrable without any significant renal structural lesions^{301 302} (see below). In cases with demonstrable excretory insufficiency, a far-reaching, even a complete restoration of kidney function can be expected after extirpation of the tumor as a possibility.^{303 304} Since infusions of epinephrine are accompanied by a diminution of renal blood flow in animal^{305 306} and human^{307 308 309}

(tachycardia, tremor, anxiety, sensation of warmth), although sometimes annoying, are not dangerous unless the injection is given too rapidly²⁵². In at least one case, the test has made it possible to detect and to remove an intra-abdominal paraganglioma after previous surgical elimination of an adrenal pheochromocytoma⁴⁵⁴.

More recently, the use of *regitine* (2-(N-p-tolyl-N-[m-hydroxyphenyl]-aminomethyl)-imidazoline hydrochloride) was introduced by Emlet, Grimson et al. ⁵⁶⁰ as a suitable drug for pheochromocytoma tests. Like benzodioxane it causes a marked fall of the blood pressure in cases of pheochromocytomatous hypertension but for a longer period of time (one to two hours). Besides, it has the advantage of not producing the unpleasant side-effects, often connected with the administration of benzodioxane and, according to the above-named workers, it can be given safely in a standard dose of 5 mg (total) for adults by the intramuscular route. In the event of an ambiguous response (patients with ordinary essential hypertension react, as a rule, with a slight depression of 10 mm Hg systolic and 8 mm diastolic on an average) the additional performance of a benzodioxane test is recommended⁵⁶⁰.

It seems worthy of note, that "false" positive benzodioxane and regitine tests were obtained in patients with uremia^{560 1175 1242, 2603 2698 2573}, the only clinical condition beside pheochromocytoma in which the regular presence of excessive amounts of circulating catecholamines (possibly epinephrine, retained because of impaired kidney function (p 312)) has been demonstrated in the blood by the writer²⁶⁷⁶.

Dibenzamine was applied by several workers as a diagnostic drug for the detection of pheochromocytomas^{160a, 3210, 3220a} but was not found sufficiently specific^{76a 1329a 3699}.

Another more primitive diagnostic aid is the provocation of paroxysms by deep massage of the adrenal region¹⁶⁹⁶. This procedure, although often ineffective and therefore unreliable, has the one advantage of permitting to determine the side on which the tumor is located, provided a positive response occurs. Palpatory detection of a pheochromocytoma is rarely possible. A flat X-ray plate or pyelogram may reveal the presence of an adrenal tumor through the criterion of downward dislocation of the kidney on the respective side. Perirenal air insufflation^{171 452 453 541 554} is likely to disclose additional details but will fail to indicate the presence of extra-adrenal paraganglia.

The pharmacological assay of sympathomimetic amines in the urine may provide a useful indication for the presence of a pheochromocytoma. It gave positive results in several cases. In one of them, an alternating prevalence of nor-epinephrine and epinephrine respectively was demonstrable^{474 475, 862}.

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demonstrable excretory insufficiency, a far-reaching, even a complete restoration of kidney function can be expected after extirpation of the tumor, as a possibility.¹⁷⁴ ²¹¹ ²¹² ²¹³ ²¹⁴ ²¹⁵ ²¹⁶ ²¹⁷ ²¹⁸ ²¹⁹ ²²⁰ ²²¹ ²²² ²²³ ²²⁴ ²²⁵ ²²⁶ ²²⁷ ²²⁸ ²²⁹ ²³⁰ ²³¹ ²³² ²³³ ²³⁴ ²³⁵ ²³⁶ ²³⁷ ²³⁸ ²³⁹ ²⁴⁰ ²⁴¹ ²⁴² ²⁴³ ²⁴⁴ ²⁴⁵ ²⁴⁶ ²⁴⁷ ²⁴⁸ ²⁴⁹ ²⁵⁰ ²⁵¹ ²⁵² ²⁵³ ²⁵⁴ ²⁵⁵ ²⁵⁶ ²⁵⁷ ²⁵⁸ ²⁵⁹ ²⁶⁰ ²⁶¹ ²⁶² ²⁶³ ²⁶⁴ ²⁶⁵ ²⁶⁶ ²⁶⁷ ²⁶⁸ ²⁶⁹ ²⁷⁰ ²⁷¹ ²⁷² ²⁷³ ²⁷⁴ ²⁷⁵ ²⁷⁶ ²⁷⁷ ²⁷⁸ ²⁷⁹ ²⁸⁰ ²⁸¹ ²⁸² ²⁸³ ²⁸⁴ ²⁸⁵ ²⁸⁶ ²⁸⁷ ²⁸⁸ ²⁸⁹ ²⁹⁰ ²⁹¹ ²⁹² ²⁹³ ²⁹⁴ ²⁹⁵ ²⁹⁶ ²⁹⁷ ²⁹⁸ ²⁹⁹ ³⁰⁰ ³⁰¹ ³⁰² ³⁰³ ³⁰⁴ ³⁰⁵ ³⁰⁶ ³⁰⁷ ³⁰⁸ ³⁰⁹ ³¹⁰ ³¹¹ ³¹² ³¹³ ³¹⁴ ³¹⁵ ³¹⁶ ³¹⁷ ³¹⁸ ³¹⁹ ³²⁰ ³²¹ ³²² ³²³ ³²⁴ ³²⁵ ³²⁶ ³²⁷ ³²⁸ ³²⁹ ³³⁰ ³³¹ ³³² ³³³ ³³⁴ ³³⁵ ³³⁶ ³³⁷ ³³⁸ ³³⁹ ³⁴⁰ ³⁴¹ ³⁴² ³⁴³ ³⁴⁴ ³⁴⁵ ³⁴⁶ ³⁴⁷ ³⁴⁸ ³⁴⁹ ³⁵⁰ ³⁵¹ ³⁵² ³⁵³ ³⁵⁴ ³⁵⁵ ³⁵⁶ ³⁵⁷ ³⁵⁸ ³⁵⁹ ³⁶⁰ ³⁶¹ ³⁶² ³⁶³ ³⁶⁴ ³⁶⁵ ³⁶⁶ ³⁶⁷ ³⁶⁸ ³⁶⁹ ³⁷⁰ ³⁷¹ ³⁷² ³⁷³ ³⁷⁴ ³⁷⁵ ³⁷⁶ ³⁷⁷ ³⁷⁸ ³⁷⁹ ³⁸⁰ ³⁸¹ ³⁸² ³⁸³ ³⁸⁴ ³⁸⁵ ³⁸⁶ ³⁸⁷ ³⁸⁸ ³⁸⁹ ³⁹⁰ ³⁹¹ ³⁹² ³⁹³ ³⁹⁴ ³⁹⁵ ³⁹⁶ ³⁹⁷ ³⁹⁸ ³⁹⁹ ⁴⁰⁰ ⁴⁰¹ ⁴⁰² ⁴⁰³ ⁴⁰⁴ ⁴⁰⁵ ⁴⁰⁶ ⁴⁰⁷ ⁴⁰⁸ ⁴⁰⁹ ⁴¹⁰ ⁴¹¹ ⁴¹² ⁴¹³ ⁴¹⁴ ⁴¹⁵ ⁴¹⁶ ⁴¹⁷ ⁴¹⁸ ⁴¹⁹ ⁴²⁰ ⁴²¹ ⁴²² ⁴²³ ⁴²⁴ ⁴²⁵ ⁴²⁶ ⁴²⁷ ⁴²⁸ ⁴²⁹ ⁴³⁰ ⁴³¹ ⁴³² ⁴³³ ⁴³⁴ ⁴³⁵ ⁴³⁶ ⁴³⁷ ⁴³⁸ ⁴³⁹ ⁴⁴⁰ ⁴⁴¹ ⁴⁴² ⁴⁴³ ⁴⁴⁴ ⁴⁴⁵ ⁴⁴⁶ ⁴⁴⁷ ⁴⁴⁸ ⁴⁴⁹ ⁴⁵⁰ ⁴⁵¹ ⁴⁵² ⁴⁵³ ⁴⁵⁴ ⁴⁵⁵ ⁴⁵⁶ ⁴⁵⁷ ⁴⁵⁸ ⁴⁵⁹ ⁴⁶⁰ ⁴⁶¹ ⁴⁶² ⁴⁶³ ⁴⁶⁴ ⁴⁶⁵ ⁴⁶⁶ ⁴⁶⁷ ⁴⁶⁸ ⁴⁶⁹ ⁴⁷⁰ ⁴⁷¹ ⁴⁷² ⁴⁷³ ⁴⁷⁴ ⁴⁷⁵ ⁴⁷⁶ ⁴⁷⁷ ⁴⁷⁸ ⁴⁷⁹ ⁴⁸⁰ ⁴⁸¹ ⁴⁸² ⁴⁸³ ⁴⁸⁴ ⁴⁸⁵ ⁴⁸⁶ ⁴⁸⁷ ⁴⁸⁸ ⁴⁸⁹ ⁴⁹⁰ ⁴⁹¹ ⁴⁹² ⁴⁹³ ⁴⁹⁴ ⁴⁹⁵ ⁴⁹⁶ ⁴⁹⁷ ⁴⁹⁸ ⁴⁹⁹ ⁵⁰⁰ ⁵⁰¹ ⁵⁰² ⁵⁰³ ⁵⁰⁴ ⁵⁰⁵ ⁵⁰⁶ ⁵⁰⁷ ⁵⁰⁸ ⁵⁰⁹ ⁵¹⁰ ⁵¹¹ ⁵¹² ⁵¹³ ⁵¹⁴ ⁵¹⁵ ⁵¹⁶ ⁵¹⁷ ⁵¹⁸ ⁵¹⁹ ⁵²⁰ ⁵²¹ ⁵²² ⁵²³ ⁵²⁴ ⁵²⁵ ⁵²⁶ ⁵²⁷ ⁵²⁸ ⁵²⁹ ⁵³⁰ ⁵³¹ ⁵³² ⁵³³ ⁵³⁴ ⁵³⁵ ⁵³⁶ ⁵³⁷ ⁵³⁸ ⁵³⁹ ⁵⁴⁰ ⁵⁴¹ ⁵⁴² ⁵⁴³ ⁵⁴⁴ ⁵⁴⁵ ⁵⁴⁶ ⁵⁴⁷ ⁵⁴⁸ ⁵⁴⁹ ⁵⁵⁰ ⁵⁵¹ ⁵⁵² ⁵⁵³ ⁵⁵⁴ ⁵⁵⁵ ⁵⁵⁶ ⁵⁵⁷ ⁵⁵⁸ ⁵⁵⁹ ⁵⁶⁰ ⁵⁶¹ ⁵⁶² ⁵⁶³ ⁵⁶⁴ ⁵⁶⁵ ⁵⁶⁶ ⁵⁶⁷ ⁵⁶⁸ ⁵⁶⁹ ⁵⁷⁰ ⁵⁷¹ ⁵⁷² ⁵⁷³ ⁵⁷⁴ ⁵⁷⁵ ⁵⁷⁶ ⁵⁷⁷ ⁵⁷⁸ ⁵⁷⁹ ⁵⁸⁰ ⁵⁸¹ ⁵⁸² ⁵⁸³ ⁵⁸⁴ ⁵⁸⁵ ⁵⁸⁶ ⁵⁸⁷ ⁵⁸⁸ ⁵⁸⁹ ⁵⁹⁰ ⁵⁹¹ ⁵⁹² ⁵⁹³ ⁵⁹⁴ ⁵⁹⁵ ⁵⁹⁶ ⁵⁹⁷ ⁵⁹⁸ ⁵⁹⁹ ⁶⁰⁰ ⁶⁰¹ ⁶⁰² ⁶⁰³ ⁶⁰⁴ ⁶⁰⁵ ⁶⁰⁶ ⁶⁰⁷ ⁶⁰⁸ ⁶⁰⁹ ⁶¹⁰ ⁶¹¹ ⁶¹² ⁶¹³ ⁶¹⁴ ⁶¹⁵ ⁶¹⁶ ⁶¹⁷ ⁶¹⁸ ⁶¹⁹ ⁶²⁰ ⁶²¹ ⁶²² ⁶²³ ⁶²⁴ ⁶²⁵ ⁶²⁶ ⁶²⁷ ⁶²⁸ ⁶²⁹ ⁶³⁰ ⁶³¹ ⁶³² ⁶³³ ⁶³⁴ ⁶³⁵ ⁶³⁶ ⁶³⁷ ⁶³⁸ ⁶³⁹ ⁶⁴⁰ ⁶⁴¹ ⁶⁴² ⁶⁴³ ⁶⁴⁴ ⁶⁴⁵ ⁶⁴⁶ ⁶⁴⁷ ⁶⁴⁸ ⁶⁴⁹ ⁶⁵⁰ ⁶⁵¹ ⁶⁵² ⁶⁵³ ⁶⁵⁴ ⁶⁵⁵ ⁶⁵⁶ ⁶⁵⁷ ⁶⁵⁸ ⁶⁵⁹ ⁶⁶⁰ ⁶⁶¹ ⁶⁶² ⁶⁶³ ⁶⁶⁴ ⁶⁶⁵ ⁶⁶⁶ ⁶⁶⁷ ⁶⁶⁸ ⁶⁶⁹ ⁶⁷⁰ ⁶⁷¹ ⁶⁷² ⁶⁷³ ⁶⁷⁴ ⁶⁷⁵ ⁶⁷⁶ ⁶⁷⁷ ⁶⁷⁸ ⁶⁷⁹ ⁶⁸⁰ ⁶⁸¹ ⁶⁸² ⁶⁸³ ⁶⁸⁴ ⁶⁸⁵ ⁶⁸⁶ ⁶⁸⁷ ⁶⁸⁸ ⁶⁸⁹ ⁶⁹⁰ ⁶⁹¹ ⁶⁹² ⁶⁹³ ⁶⁹⁴ ⁶⁹⁵ ⁶⁹⁶ ⁶⁹⁷ ⁶⁹⁸ ⁶⁹⁹ ⁷⁰⁰ ⁷⁰¹ ⁷⁰² ⁷⁰³ ⁷⁰⁴ ⁷⁰⁵ ⁷⁰⁶ ⁷⁰⁷ ⁷⁰⁸ ⁷⁰⁹ ⁷¹⁰ ⁷¹¹ ⁷¹² ⁷¹³ ⁷¹⁴ ⁷¹⁵ ⁷¹⁶ ⁷¹⁷ ⁷¹⁸ ⁷¹⁹ ⁷²⁰ ⁷²¹ ⁷²² ⁷²³ ⁷²⁴ ⁷²⁵ ⁷²⁶ ⁷²⁷ ⁷²⁸ ⁷²⁹ ⁷³⁰ ⁷³¹ ⁷³² ⁷³³ ⁷³⁴ ⁷³⁵ ⁷³⁶ ⁷³⁷ ⁷³⁸ ⁷³⁹ ⁷⁴⁰ ⁷⁴¹ ⁷⁴² ⁷⁴³ ⁷⁴⁴ ⁷⁴⁵ ⁷⁴⁶ ⁷⁴⁷ ⁷⁴⁸ ⁷⁴⁹ ⁷⁵⁰ ⁷⁵¹ ⁷⁵² ⁷⁵³ ⁷⁵⁴ ⁷⁵⁵ ⁷⁵⁶ ⁷⁵⁷ ⁷⁵⁸ ⁷⁵⁹ ⁷⁶⁰ ⁷⁶¹ ⁷⁶² ⁷⁶³ ⁷⁶⁴ ⁷⁶⁵ ⁷⁶⁶ ⁷⁶⁷ ⁷⁶⁸ ⁷⁶⁹ ⁷⁷⁰ ⁷⁷¹ ⁷⁷² ⁷⁷³ ⁷⁷⁴ ⁷⁷⁵ ⁷⁷⁶ ⁷⁷⁷ ⁷⁷⁸ ⁷⁷⁹ ⁷⁸⁰ ⁷⁸¹ ⁷⁸² ⁷⁸³ ⁷⁸⁴ ⁷⁸⁵ ⁷⁸⁶ ⁷⁸⁷ ⁷⁸⁸ ⁷⁸⁹ ⁷⁹⁰ ⁷⁹¹ ⁷⁹² ⁷⁹³ ⁷⁹⁴ ⁷⁹⁵ ⁷⁹⁶ ⁷⁹⁷ ⁷⁹⁸ ⁷⁹⁹ ⁸⁰⁰ ⁸⁰¹ ⁸⁰² ⁸⁰³ ⁸⁰⁴ ⁸⁰⁵ ⁸⁰⁶ ⁸⁰⁷ ⁸⁰⁸ ⁸⁰⁹ ⁸¹⁰ ⁸¹¹ ⁸¹² ⁸¹³ ⁸¹⁴ ⁸¹⁵ ⁸¹⁶ ⁸¹⁷ ⁸¹⁸ ⁸¹⁹ ⁸²⁰ ⁸²¹ ⁸²² ⁸²³ ⁸²⁴ ⁸²⁵ ⁸²⁶ ⁸²⁷ ⁸²⁸ ⁸²⁹ ⁸³⁰ ⁸³¹ ⁸³² ⁸³³ ⁸³⁴ ⁸³⁵ ⁸³⁶ ⁸³⁷ ⁸³⁸ ⁸³⁹ ⁸⁴⁰ ⁸⁴¹ ⁸⁴² ⁸⁴³ ⁸⁴⁴ ⁸⁴⁵ ⁸⁴⁶ ⁸⁴⁷ ⁸⁴⁸ ⁸⁴⁹ ⁸⁵⁰ ⁸⁵¹ ⁸⁵² ⁸⁵³ ⁸⁵⁴ ⁸⁵⁵ ⁸⁵⁶ ⁸⁵⁷ ⁸⁵⁸ ⁸⁵⁹ ⁸⁶⁰ ⁸⁶¹ ⁸⁶² ⁸⁶³ ⁸⁶⁴ ⁸⁶⁵ ⁸⁶⁶ ⁸⁶⁷ ⁸⁶⁸ ⁸⁶⁹ ⁸⁷⁰ ⁸⁷¹ ⁸⁷² ⁸⁷³ ⁸⁷⁴ ⁸⁷⁵ ⁸⁷⁶ ⁸⁷⁷ ⁸⁷⁸ ⁸⁷⁹ ⁸⁸⁰ ⁸⁸¹ ⁸⁸² ⁸⁸³ ⁸⁸⁴ ⁸⁸⁵ ⁸⁸⁶ ⁸⁸⁷ ⁸⁸⁸ ⁸⁸⁹ ⁸⁹⁰ ⁸⁹¹ ⁸⁹² ⁸⁹³ ⁸⁹⁴ ⁸⁹⁵ ⁸⁹⁶ ⁸⁹⁷ ⁸⁹⁸ ⁸⁹⁹ ⁹⁰⁰ ⁹⁰¹ ⁹⁰² ⁹⁰³ ⁹⁰⁴ ⁹⁰⁵ ⁹⁰⁶ ⁹⁰⁷ ⁹⁰⁸ ⁹⁰⁹ ⁹¹⁰ ⁹¹¹ ⁹¹² ⁹¹³ ⁹¹⁴ ⁹¹⁵ ⁹¹⁶ ⁹¹⁷ ⁹¹⁸ ⁹¹⁹ ⁹²⁰ ⁹²¹ ⁹²² ⁹²³ ⁹²⁴ ⁹²⁵ ⁹²⁶ ⁹²⁷ ⁹²⁸ ⁹²⁹ ⁹³⁰ ⁹³¹ ⁹³² ⁹³³ ⁹³⁴ ⁹³⁵ ⁹³⁶ ⁹³⁷ ⁹³⁸ ⁹³⁹ ⁹⁴⁰ ⁹⁴¹ ⁹⁴² ⁹⁴³ ⁹⁴⁴ ⁹⁴⁵ ⁹⁴⁶ ⁹⁴⁷ ⁹⁴⁸ ⁹⁴⁹ ⁹⁵⁰ ⁹⁵¹ ⁹⁵² ⁹⁵³ ⁹⁵⁴ ⁹⁵⁵ ⁹⁵⁶ ⁹⁵⁷ ⁹⁵⁸ ⁹⁵⁹ ⁹⁶⁰ ⁹⁶¹ ⁹⁶² ⁹⁶³ ⁹⁶⁴ ⁹⁶⁵ ⁹⁶⁶ ⁹⁶⁷ ⁹⁶⁸ ⁹⁶⁹ ⁹⁷⁰ ⁹⁷¹ ⁹⁷² ⁹⁷³ ⁹⁷⁴ ⁹⁷⁵ ⁹⁷⁶ ⁹⁷⁷ ⁹⁷⁸ ⁹⁷⁹ ⁹⁸⁰ ⁹⁸¹ ⁹⁸² ⁹⁸³ ⁹⁸⁴ ⁹⁸⁵ ⁹⁸⁶ ⁹⁸⁷ ⁹⁸⁸ ⁹⁸⁹ ⁹⁹⁰ ⁹⁹¹ ⁹⁹² ⁹⁹³ ⁹⁹⁴ ⁹⁹⁵ ⁹⁹⁶ ⁹⁹⁷ ⁹⁹⁸ ⁹⁹⁹ ¹⁰⁰⁰

^{2781a}, and since nor-epinephrine acts in the same fashion^{288a}, it seems probable that the renal functional changes in cases of pheochromocytoma are initiated by such a mechanism. During hypertensive crises, marked renal vasoconstriction with a five-fold rise of efferent arteriolar resistance has been observed⁹⁷¹.

Episodes of "paroxysmal nephropathy" may reveal the presence of a pheochromocytoma even in otherwise asymptomatic cases⁹⁷¹.

Cardiac Manifestations (Functional)

During acute attacks, the heart rate is usually markedly increased. There may be 170 or more beats per minute (lit., see ¹⁴³⁶ ²⁶⁵⁹) but, on the other hand, also bradycardia of 60 beats or less has been seen to occur during hypertensive paroxysms¹⁴³⁶, ²¹⁷³, ²²⁶⁷ ²³⁹⁴ ²⁴⁵⁵, ²⁵¹⁷ ²⁶³⁰. This latter phenomenon is undoubtedly due to secondary vagal stimulation, mediated by the pressor receptor organs. It constitutes a characteristic effect also of injected or infused nor-epinephrine (p. 9). Patients with chronic pheochromocytomatous hypertension display, as a rule, a slightly to moderately accelerated heart action (90-130 beats per minute) which may or may not be associated with the subjective sensation of palpitations. Some patients show marked cardiac acceleration when an upright position is assumed²⁷¹⁹, ³¹⁷⁶. Sinus arrhythmias have also been observed¹⁴³⁶.

Cardiac arrhythmias are a common occurrence during and immediately after acute paroxysms, especially extrasystoles and auricular fibrillation⁹⁹⁹, ⁹⁰⁰ ¹⁰⁶⁰ ¹⁴³⁶; furthermore, sinoauricular block¹⁴³⁷, atrioventricular⁹⁰⁰ ¹⁴³⁶ ²¹⁴⁴ and other types of ectopic rhythms, such as wandering pacemaker and dissociations with interference⁴³⁸ ⁹⁰⁰ ¹⁴³⁶ ²²⁹⁴. Some of these arrhythmias can be interpreted as the results of a combined primary sympathetic and simultaneous secondary vagal stimulation.

The hypoxia-producing chemical action of excessive amounts of circulating epinephrine and nor-epinephrine upon myocardial metabolism manifests itself by the appearance of the so-called "anoxia" pattern of the electrocardiogram during paroxysms, as well as by the constant presence of this pattern in some cases of sustained pheochromocytomatous hypertension: flattening or inversion of the T-wave in one or more leads and an occasional depression of the S-T interval⁴³⁵ ⁹⁰⁰ ¹²⁴⁴ ¹⁴³⁶ ¹⁵⁴⁷ ²²⁶⁷ ²³³⁴ ²⁵¹⁷ ²⁷¹⁹ ²⁸³³ ³⁴⁷⁹. Although these changes of the electrocardiogram are often interpreted as being caused by the mechanical strain imposed upon the heart by the "burden" of an elevated blood pressure, it could be shown²⁷¹² that the changes of the T-wave and the S-T segment, which are typically elicited by epinephrine¹⁹⁶⁰ ¹⁹⁶² ³¹⁶⁵, occur in complete independence of the blood pressure level. Consequently, it appears probable that the "strain pattern" of the electrocardiogram, as seen in pheochromocytoma cases, represents a

biochemical interference on the part of the circulating sympathomimetic amines in the electrophysical status of the myocardium. Electrocardiographic changes, induced by a single paroxysm, may persist for days afterwards.¹⁴⁴ Additional myocardial injury is to be expected, of course, in those older cases which develop coronary sclerosis and marked ventricular hypertrophy. Alterations of the P-wave and of the QRS complex and a prolonged Q-T duration have been described by several observers.^{145, 146, 147, 214, 215} Removal of the tumor leads to normalization of the electrocardiogram⁷¹⁹ unless permanent structural damage to the heart muscle has developed previously.

The most distressing cardiac symptom which complicates pheochromocytoma-induced paroxysms is substernal and epigastric pain of the anginal type.^{149, 154, 155, 143, 195, 242, 243, 259} It is obviously caused by the hypoxia-producing chemical effect^{150, 216, 159, 159a, 225} of epinephrine and nor-epinephrine upon the heart muscle (p. 11 ff.) and it is identical in principle with the anginal attacks elicited by injections of large doses of epinephrine in young healthy individuals.^{243, 246}

(c)

no

or

181. however, accompanies many of the severe hypertensive paroxysms and constitutes one of their most dangerous complications.^{204, 147, 154} Although the exact mechanism of the origin of pulmonary edema is still problematical²⁰⁴, it is known that this condition can be readily elicited in animals by the injection of large doses of epinephrine^{184, 210, 219, 220} and still larger ones of nor-epinephrine.²¹⁰ It does not seem too far-fetched, therefore, to assume an analogous mechanism to operate in the pulmonary edema of pheochromocytoma patients.

Death from Pheochromocytoma

Death, causally related to a pheochromocytoma, may conclude a long period of illness of the sustained hypertension pattern and be due to congestive cardiac failure or uremia, but in the majority of cases it occurs rather suddenly in connection with one out of a series of hypertensive paroxysms.^{127, 173, 204, 242, 211, 205} following a surgical procedure, tooth extraction, normal labor²⁰⁵, injury to the head²⁶⁵, etc., or without any known eliciting circumstances.^{204, 242} There is hardly any reason to doubt that such fatal events are precipitated by a sudden outpour of epinephrine and nor-epinephrine from the tumor, possibly under the influence of a central nervous stimulus¹⁵⁹, and that their mechanism is similar to that by which death can be rapidly induced in animals through injection of sympathomimetic catecholamines (p. 14). The fatal attacks are usually associated

with epigastric oppression, severe dyspnea, pulmonary edema and cyanosis. Lack of pertinent observations makes it impossible to state which of the two forms of "physiological" cardiac death, namely ventricular fibrillation^{2577a} or cardiac stand-still^{2121, 2205}, is to be held responsible for the fatal outcome of pheochromocytoma cases. The former might be attributable to direct epinephrine action upon the heart, the latter to secondary overwhelming vagal stimulation.

Cerebral vascular accidents are the cause of death in only a small percentage of cases.

Morphological Cardiovascular Lesions

The ability of epinephrine to produce necrotizing and calcifying lesions of the media of large vessels, to cause myocardial degeneration, to intensify intima lipoidosis, and to stimulate via the pituitary the adrenocortical secretion of steroids which are potentially injurious to the arterioles and the heart (p. 31 ff.), makes it intelligible that pheochromocytoma cases, particularly those of long standing, often present extensive anatomical cardiovascular damage.

Generalized arteriosclerosis (atheromatosis) and arteriolosclerosis have been seen even in young children with chromaffin neoplasms^{154, 1840 1899}. In adults they are a common finding (lit., see ¹³⁹⁴). The distribution is irregular, but the renal arterioles seem to be particularly intensely involved as a rule^{1244 1437 1470 1840 2542}. Nevertheless, there is a substantial number of pheochromocytoma cases on record in which no significant morphological vascular changes were detected at necropsy^{1744 2617} despite the fact that some of them had displayed indications of functional renal involvement, such as albuminuria, reduced PSP excretion, and azotemia¹²⁴⁴, apparently on an essentially renal vasoconstrictive basis^{134 1829 2791}.

One important cause of the prominence of renal injury, both functional and anatomical, in the pheochromocytoma syndrome may be the fact that epinephrine and nor-epinephrine, partly in an active, partly in an inactive conjugated form^{252 911 946 1330 2793}, pass through the kidneys into the urine. It can be understood that the constant exposure of the renal vessels to such potentially angiotoxic material may constitute a serious threat to their functional and structural integrity, especially if abnormally large quantities are excreted, as is the case in the presence of a pheochromocytoma. Functional glomerular damage has been produced experimentally by infusions of epinephrine and nor-epinephrine^{2383a}. In a series of 42 human kidneys in which the concentration of epinephrine-like catecholamines was studied by the writer²⁶⁷¹, an excessively high reading was obtained in the kidney of a case with histologically unidentified nodules in the adrenal medulla. The blood pressure of this patient had been 218/74, the low diastolic pressure

suggesting the "stroke-volume type" of hypertension, as typically produced by epinephrine.

Hypertrophy of the heart, predominantly of the left ventricle, is another characteristic of numerous cases of pheochromocytoma, particularly of those with chronic hypertension^{205, 224, 237}; but it occurs also sometimes in paroxysmal forms with normotensive intervals^{1720 1555, 2025, 2411, 2674}. The tendency of the heart muscle to absorb eagerly and to deposit circulating sympathomimetic amines²⁶⁷⁰ is probably an important contributory factor in the development of this feature (see Fig 75)

Coronary sclerosis has been observed in pheochromocytoma patients as young as 10 years⁶²⁴ but does not seem to be a frequent finding. Degenerative and fibrotic foci in the myocardium are likewise only occasionally seen^{264 1412 2572}.

Treatment

The only permanently effective treatment for the pheochromocytoma syndrome is surgical removal of the tumor or tumors, as first performed on the basis of a correct diagnosis by Pineoffs in 1929²⁶⁰². Attempts at other forms of therapy, such as x-ray irradiation of the adrenal region^{1931 2434}, amylnitrite^{1544 2112 2120}, thyroidectomy^{412 499 1244}, or thiocrea compounds^{159 2712} were either entirely unsuccessful or gave only temporary relief. During the pre-operative period, marked symptomatic improvement was achieved by injections of dibenamine at 72-hour intervals^{2210 2220}.

A survey of 20 surgically treated cases which was published in 1938²¹¹² lists 15 patients as cured, while five died as a direct result of the operation. In another series, compiled in 1944²¹⁷¹, three deaths were reported out of 18 cases. Evidently, modern methods of preventing and counteracting the otherwise extremely dangerous side effects of the operation have diminished its hazards, as can be gathered also from more recent reports of successful surgical intervention^{771 431 1547 2440} which include one case with multiple tumors¹⁵⁰².

If the tumor is unilateral and identifiable with certainty, the extraperitoneal approach through a lumbar incision is preferred by most surgeons. On the other hand, if there is any doubt concerning location and number of neoplasms, a ventral incision and transperitoneal procedure will offer greater advantages. Spinal anesthesia should be avoided because of its vasodepressant effect^{2124 2457 2226}.

The chief dangers connected with the operation are the following: (a) extreme rises of the blood pressure, due to massive hormonal discharges from the tumor while it is being manipulated, (b) precipitous drop of the blood pressure during the operation or within the first following hours, possibly caused by the sudden deprivation of the body of its accu-tomed

with epigastric oppression, severe dyspnea, pulmonary edema and cyanosis. Lack of pertinent observations makes it impossible to state which of the two forms of "physiological" cardiac death, namely ventricular fibrillation^{2577a} or cardiac stand-still^{2421, 2305}, is to be held responsible for the fatal outcome of pheochromocytoma cases. The former might be attributable to direct epinephrine action upon the heart, the latter to secondary overwhelming vagal stimulation.

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Until several years ago, there seemed to exist certain contradictions which appeared to justify the reluctance of some skeptics to subscribe to far-reaching analogy conclusions concerning the role of adrenergic neuro-hormones in the pathogenesis of other cardiovascular diseases in which no morphological and blood-chemical equivalent to the adrenergic over-activity of a chromaffin neoplasm could be demonstrated. The greater part of these contradictions has been cleared away, however, through discovery of the following facts, which it will be necessary to keep in mind in an effort to make full use of the general information, deductible from the pheochromocytoma syndrome.

(1) The prevalent elaboration and secretion not of epinephrine but of nor-epinephrine by most of the pheochromocytomas,

(2) The hemodynamic and metabolic differences between epinephrine and nor-epinephrine, particularly the exclusively vasoconstrictor, diastolic pressor, not tachycardic and not significantly hyperglycemic properties of the latter,

(3) The chemically oxygen consumption-stimulating and thus potentially anoxia-producing effect of both epinephrine and nor-epinephrine upon cardiovascular tissue,

(4) The specific tendency of the heart muscle (and the vascular musculature?) to eagerly absorb and accumulate epinephrine and nor-epinephrine in potentially anoxia-producing concentrations,

(5) The principle of sympathetic neurosecretion, by which nor-epinephrine is being discharged directly into the cardiovascular contractile effector cells without first passing through the blood stream,

(6) The functional relationship between adrenal medulla and cortex: (a) stimulation of the cortex by epinephrine via the pituitary gland and (b) potentiation of the cardiovascular effects of both epinephrine and nor-epinephrine through adrenal mineralocorticoids

In our further deliberations concerning various aspects of cardiovascular pathology, we shall repeatedly take recourse to the following:

1. The cardiovascular pathology which are faithfully mimicked by the hormonal activity of the pheochromocytoma:

(1) essential hypertension with all its typical hemodynamic, cardiac, renal, ophthalmic and metabolic complications; (2) malignant hypertension with all its typical hemodynamic, renal, ophthalmic, cardiac and metabolic complications; (3) arteriosclerosis and arteriolesclerosis, especially nephrosclerosis; (4) pulmonary edema, (5) angina pectoris; (6) sudden "physiological" cardiac death

It is obvious that the route by which nor-epinephrine and epinephrine

supply of sympathomimetic material; (c) belated development of a severe shock syndrome within the first 48 hours, eventually ending in coma, hyperpyrexia and death. This latter condition is believed to result from adrenocortical insufficiency. Since there are no indications of a state of hypoadrenocorticism in the pre-operative phase³¹⁹⁷, except for the post-paroxysmal signs of general exhaustion, it may be assumed that the excessive flooding of the organism with epinephrine which occurs during the operation will over-stimulate the pituitary-adrenocortical system and thus deplete the hormonal reserves of the cortex which had already been taxed almost to capacity by the constant presence of an epinephrine-secreting tumor. Nor-epinephrine, by contrast, exerts only very little influence upon pituitary-cortical secretion^{1602 2182 2418 2943}.

In order to cope with the above outlined perilous situations, it is necessary to supply the patient before the operation is begun with ample doses of adrenocortical extract (which is preferable to desoxycorticosterone), to handle the tumor as gently as possible, to interrupt the procedure if the blood pressure rises to critical heights, and to infuse epinephrine (or probably better, nor-epinephrine³⁵⁸) if the blood pressure falls. Application of dibenamine, benodaine or regitine before or during surgery is useful to prevent or to alleviate hypertensive crises^{436 576b 960 1253}. The administration of epinephrine after dibenamine is useless or even harmful^{1329a 2084a}. The post-operative care requires utmost vigilance, the intramuscular administration of epinephrine in oil and adrenocortical preparations, furthermore, infusions of plasma and of hypertonic glucose in saline solution, if needed. These precautions should reduce operative mortality to a minimum and restore the pheochromocytoma patients to complete health, provided that surgery is not delayed until irreversible cardiovascular lesions have developed¹⁶⁹.

Heuristic Aspects of the Pheochromocytomatous Cardiovascular Syndrome

Despite its comparative rarity, the pheochromocytoma-induced syndrome is suited to occupy a key position of the first order in the entire structure of up-to-date reasoning in regard to the pathogenic mechanism of several of the most common and practically most important diseases of the cardiovascular system. What artificial animal experimentation has attempted time and again with crude and inadequate means and with only fragmentary success, namely the establishment of a state of chronic overactivity of the sympathomimetic neurohormones, was obligingly achieved by Nature herself in human subjects by creating the pheochromocytoma as the crucial experiment, necessary for the understanding of a variety of other morbid entities.

cortex which are suggestive of cortical over-function, such as tumors or simple hyperplasia, these cortical abnormalities and their influence upon the cardiovascular system will be discussed in the same section.

A causal connection between the presence in the human body of an adrenocortical tumor and hypertension was first recognized by Neusser in 1898. Josué was the first to point out the co-existence of contracted kidneys and enlarged lipid-rich adrenal cortices (1901). Since then, interest in the role of the adrenal cortex in cardiovascular pathology has steadily grown. It received strong impulses in 1932 through Cushing's description of the syndrome which bears his name, and more recently through the chemical identification of various cortical steroids and the study of their influence upon electrolyte metabolism¹¹⁶ and cardiovascular function.

Among the adrenal cortical tumors there are those benign growths which remain clinically symptomless, others of a benign or malignant character which produce endocrine manifestations exclusively in the sexual sphere, and finally those benign or malignant cortical neoplasms whose hormonal effects concern both the sexual characteristics and other bodily structures, e.g. the cardiovascular system, or the latter primarily. In the following discussion we shall concentrate our attention on the tumors of the cortex whose endocrine activity is known to affect the cardiovascular system, whereas similar growths with a prevailingly virilizing effect will be considered only insofar as they show some degree of cardiovascular involvement. The clinical entities which represent the two functional extremes are designated as "Cushing's syndrome" on one hand, and the "adrenogenital syndrome" on the other. It must be borne in mind, however, that considerable over-lapping between their respective symptoms is often seen¹¹⁷⁻¹²⁰ so that it is impossible to draw a sharp dividing line between them.

Endocrine Pathology

The morphological findings obtained in individuals who during their lifetime had presented either the adrenogenital syndrome or Cushing's syndrome, or combinations of both, have been critically analyzed by Soffer¹²¹ and by Kepler.¹²² In surveying the accumulated case reports, one is struck by two rather confusing features, namely (a) the irregularity of the relation between the degrees of anatomical anomalies and of functional derangement and (b) the close, but likewise quite irregular connections between anatomical alterations of the adrenal cortex and the anterior pituitary in these disorders.

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pe . . . who have been afflicted with this disease may reveal both benign and malignant tumors (appr. 20 per cent)¹²³⁻¹²⁶ or only hyperplasia (appr.

the necropsy of

gain access to their cardiovascular target cells must be a different one in the case of pheochromocytoma on the one hand (blood stream) and in the case of ubiquitous sympathetic postganglionic neurosecretion (local discharges into effector cells). It is also very probable that exaggerated adrenergic neurohormonal effects do not occur exclusively on the basis of an excess formation of the respective neurohormones, but that they may likewise arise by way of an abnormally increased responsiveness of their target cells under the potentiating influence of other hormones (thyroid, corticoids). Nevertheless, it would be far-fetched in the light of present-day knowledge not to regard the nature of the above listed cardiovascular syndromes from the point of view of their fundamental analogy with the phenomena of adrenergic neurohormonal over-action. It would also be more difficult by this time to present evidence against a dominating role of the endocrine system in general and of the sympathomimetic catecholamines in particular in various common forms of cardiovascular pathology than it is to point out its conspicuous probability.

Summary

The cardiovascular manifestations, attributable to the secretion of excess amounts of *nor*-epinephrine and epinephrine by chromaffin tumors, consist of paroxysmal or sustained arterial hypertension, vasoconstrictive injury of the kidney, vascular ocular lesions, cardiac arrhythmias, anginal symptoms, pulmonary edema, congestive heart failure, arteriosclerotic and arteriolo-sclerotic vascular changes, especially of the kidneys, cardiac hypertrophy, and sudden cardiac death. All these pathological conditions, with the exception of irreversibly established anatomic lesions and death, disappear promptly and completely after timely removal of the tumor or tumors. A secondary functional involvement of the adrenal cortex and of the diencephalon in the pheochromocytoma-induced syndrome, although not definitely proven, must be thought of as a possibility.

The pheochromocytoma represents one compact and radically removable source of circulating excess sympathomimetic catecholamines, in contrast to the ubiquitous adrenergic neurosecretory discharges into cardiovascular effector cells which are probably involved in other cardiovascular disorders. Nevertheless, one can consider the pheochromocytoma syndrome as a most instructive "experiment", devised by Nature for the indirect pathogenic evaluation of some common cardiovascular diseases, such as essential and malignant hypertension, nephrosclerosis, "hypertensive" heart disease, angina pectoris, pulmonary edema, and others.

Adrenocortical Tumors and Hyperplasia

Since identical clinical cardiovascular disturbances have been observed in persons showing different types of morphological changes of the adrenal

noma without the concomitant presence of the syndrome is probably due to the fact that those functions of the involved glands are not altered. It may very well be that certain cells of the adrenal cortex, for example, perform certain specific functions, and unless the cells are directly or indirectly involved, no alteration of those particular functions will occur." Besides, there remains the theoretical possibility that in the absence of abnormalities of hormone production on the part of the adrenal cortex itself, an alteration of the selective corticoid-inactivations by the liver²²¹, ²²⁶ might result in a disturbance of equilibrium of corticoid actions.

A survey of the sex distribution of Cushing's syndrome revealed a marked prevalence of the disease in women²²⁴. Some of the pathogenic tumors arise from accessory cortical tissue^{223, 227}, some are bilateral^{223, 230, 231}. In the more common cases of unilateral cortical tumors, the contralateral cortex tends to become atrophic^{223, 240, 246, 247, 250}, probably due to inhibitory effects exerted by the over-active hormones of the tumor upon the elaboration of adrenocorticotrophic hormone in the anterior pituitary.

Hyperplastic changes of the thyroid, the parathyroids and the thymus, which are occasionally seen in connection with the adrenocortical syndromes^{1192, 1732, 2026}, are to be regarded as accidental secondary phenomena rather than as basically significant factors in the pathogenic mechanisms of these syndromes.

There exists a multitude of environmental and nutritional factors which can give rise to adrenocortical enlargement²⁴⁸ but whose specific significance for the development of Cushing's syndrome has not yet been evaluated.

Hormone Production and Secretion; Diagnostic Procedures

of
the
... constitute the most important groups, as far as their ... that such a variety of hormone will permit a wide range of ... disturbances to occur in accordance with the number of possible combinations of individual hormonal over- and under-productions and with their varying rebound effects upon the pituitary gland. Only the group of the "..." (estrogens and androgens), including the ... which are somewhat arbitrarily designated ... an

60 per cent)²⁴⁴ of the cortex or no recognizable cortical pathology at all (ca. 20 per cent)^{169, 1731, 2155, 2451, 2492}. The frequent co-existence of basophil adenomas of the anterior pituitary with Cushing's syndrome³²³⁰ introduces another element of uncertainty into the pathogenic evaluation of the clinical picture. Indeed, for some time, Cushing's syndrome was believed to be a disease of straight pituitary origin. However, this conception has been largely abandoned in favor of the assumption of a prevalingly adrenocortical disturbance^{1731, 3157} which is supported by the following observations: (a) in all of 24 cases of basophil adenomas of the pituitary which did not display the Cushing syndrome, the adrenals appeared normal²⁴⁵¹; (b) surgical removal of a cortical tumor is apt to abolish the clinical symptoms^{1731, 3501}; (c) typical signs of Cushing's syndrome can be provoked by the administration of the cortical steroid cortisone, as well as by the adrenocorticotrophic hormone ACTH³³⁹⁴.

A hypothesis which contends that the basophil cells are the physiological source of the adrenocorticotrophic factor of the pituitary¹⁸³⁴ has not been convincingly proven; neither can this be said of Heinecker's interesting but highly speculative doctrine, according to which an adrenocortical over-activity would be caused by a preponderance of the eosinophils of the anterior pituitary, resulting from degenerative alterations⁸¹⁵ of the basophil cells which, in turn, are ascribed to an atrophy of the paraventricular nuclei whose integrity is supposed to be a pre-requisite for maintenance of the normal functional and trophic state of the basophils by means of the hormones issuing from the neurohypophysis^{941, 1440}. The facts that cortisone over-dosage produces similar hypothalamic changes⁴⁹¹ and that absolute over-function of the eosinophils (acromegaly) does not typically elicit the clinical features of Cushing's syndrome, are hardly compatible with Heinecker's and Findley's hypothesis even though a coexistence of acromegaly and Cushing's syndrome has been observed in a few isolated cases²¹²⁴.

All possible combinations of simultaneous or alternative presence and absence of anatomical anomalies of the adrenal cortex (tumors, hyperplasia) and of the anterior pituitary (basophil adenomas, diffuse proliferation of hyalinized cells⁶¹⁵, chromophobe, acidophile and other unclassified tumors (lit., see ³¹⁵⁷, also ¹⁴²⁰)) are encountered in patients with Cushing's syndrome, even neoplasms of the thymus have been observed in such cases^{1753, 2025}. In view of this bewildering maze of seemingly conflicting evidences, Soffer²¹⁵⁷ arrives at the following sober appraisal of the widely over-rated validity of purely morphological criteria in the interpretation of abnormal functional states: "Extensive distortions in the physiology of the endocrines can be present without any concomitant gross or microscopic abnormalities of the various glands, determined by our present pathological methods. Similarly, the presence of a tumor of the adrenal cortex or of a basophil ade-

Quantitative estimations of the excretion of adrenocorticotrophic pituitary hormone with the urine have been carried out in only a few cases of Cushing's syndrome up to the present. Some of the results seemed to indicate an increased production of this hormone¹⁶⁵, while others did not²⁶⁶.

The ACTH and epinephrine eosinopenia tests^{225, 229}, while useful for the diagnosis of adrenal hypofunction, do not seem to contribute much to that of hyperadrenocorticism, but absolutely low eosinophil counts may be diagnostically helpful.

The blood concentration of epinephrine-like catecholamines in patients with Cushing's syndrome was found by the writer to be near or slightly above the upper level of the normal range²⁶⁷.

The techniques and results of x-ray exploration by flat plate, pyelogram, or perirenal air insufflation^{157, 268} are similar to those mentioned in connection with the adrenal pheochromocytomas^{152, 244, 246}.

General Symptomatology

The classical picture of Cushing's syndrome may develop at any age between early childhood and the beginning of sexual involution, with a male to female proportion of about one to three^{174, 267}. It is composed of a remarkably bizarre variety of somatic anomalies²⁶⁷. Some of them are so conspicuous that they greatly facilitate the diagnosis, even without extensive laboratory work. Perhaps the most striking peculiarity are the dark, purplish striae on abdomen, hips, thighs, shoulders and breasts which, although not absolutely specific and although not present without exception, may be considered as nearly definite proof of existing hyperadrenocorticism of the Cushing type (Fig. 13). In a series of 33 cases, obesity was reported 28 times²⁶⁷. It is often limited to the trunk, neck and face, the so-called "full-moon face" or "buffalo type", and may leave the extremities unaffected. In some patients, it developed with surprising rapidity over a period of weeks. Hypertrichosis and masculine hair distribution are frequently observed in females and prepuberal males. Hypertrophy of the clitoris develops only in those cases which approach the adrenogenital syndrome. The same is true for baldness of the head in women. Female patients give a history of dysmenorrhea or amenorrhea. There is also reduced libido or complete impotence. Apart from the striae, the skin is often involved, in that the face assumes a copper-red or dusky hue with acne pustules, while acrocyanosis and ecchymoses appear on the extremities. The skin is highly susceptible to purulent infections. Osteoporosis may complicate the picture by causing a kyphotic deformation of the spine and intense radicular pains. The patients complain of weakness, fatigue, and

culty. At the present time, no convenient direct assay method is available, but the recently introduced analysis of the *electrolyte composition of thermal sweat*, collected from either the hand, forearm and abdomen⁵⁷² or from one forearm alone^{1976, 2067}, seems to offer the most promising approach to this important field of investigation. An increased activity of the desoxycorticosterone-like salt-retaining steroids is reflected in a sharp decline of the sodium concentration of the thermal sweat even more conclusively than this is the case in the urine⁵⁷². The first results obtained with this method in patients with Cushing's syndrome revealed a very low sodium and chloride concentration in sweat⁵⁷². Similar findings have been reported in hypertensive patients with "pseudo-Cushing" syndrome⁵⁷⁶. This latter condition will be discussed on p 284.

There are several chemical^{689, 2210, 2244} and biological^{32, 341, 2481} methods in existence for the *assay of the urinary excretion of the total corticoids* or the carbohydrate-active 11-oxy steroid group to which a substantial part of the clinical features of Cushing's syndrome is ascribed. As was to be expected, several investigators^{156, 1017, 2246, 2247, 2464} obtained abnormally high readings with these methods in patients with hyperadrenocorticism, e.g., a 12-fold increase above normal²⁴⁶⁴; but in some exceptional "inactive" cases also normal values were found²⁴⁶⁴. The complicatedness and expense of these procedures has so far prevented their introduction into general laboratory practice. The presence of corticoids has been demonstrated also in the blood of patients with Cushing's syndrome¹²²⁰.

Normally, the daily excretion of total corticoids is approximately 700 gamma, one-fifth of which consists of mineralocorticoids²⁵⁵⁰.

By far the most widely used techniques for the assay of steroid excretion are the various colorimetric determinations of 17-ketosteroids (androgens) in the urine. Their value in regard to the pathogenic diagnosis of Cushing's syndrome and of its cardiovascular complications is a limited one, however, in that numerous cases in which an abnormal production of sexual cortical steroids is not involved, yield normal or only slightly elevated figures^{1039, 1753, 2464}, quite apart from a certain inaccuracy inherent in the participation of gonadal 17-ketosteroids in the results, obtained in the male. The normal range in the female is 6-18 mg per 24 hours with an average of 12 mg, in the male 10-25 mg per 24 hours with an average of 17 mg²⁴⁶⁴. While normal readings do not rule out the presence of a genuine Cushing syndrome, its clinical recognition is facilitated by definitely elevated values. A more specific analysis of various 17-ketosteroid fractions may permit certain conclusions in regard to the differentiation between tumors and simple hyperplasia of the adrenal cortex²⁹²⁰.

Estrogens have also been found in increased amounts in the urine of some such patients^{253, 1753}, occasionally even of males²⁰⁰⁶.

electrolyte levels in some of his cases may be explained by the variability of the quantitative steroid distribution in hyperadrenocorticism which does not always necessarily involve the mineralocorticoids as profoundly as the glucocorticoids, to which many of the clinical features owe their existence. Besides, there are some indications of a mutual interplay of the mineralo- and glucocorticoids, regarding electrolyte metabolism (p. 29) which may very well account for certain irregularities of the serum electrolyte pattern. This point is illustrated by the paradoxical effect of DCA in patients with Cushing's syndrome in whom this substance apparently rather favors than inhibits the urinary excretion of sodium²¹²². In general, however, the urinary excretion of sodium seems to be subnormal in Cushing's syndrome, while potassium is eliminated in large quantities¹¹²³, which would be in keeping with the postulated over-action of desoxycorticosterone-like steroids. Altogether, it can be said that with some still problematical exceptions, the behavior of sodium and potassium in hyperadrenocorticism shows distinct analogies with the effects of artificially administered DCA and that these make it appear legitimate to incorporate some of the experimental results obtained with DCA into our rationalizing concerning the origin of the cardiovascular anomalies which form an integral part of Cushing's syndrome and of related clinical states.

It might be further mentioned that beside a diminution of serum chloride, alkalosis is a common occurrence in Cushing's syndrome^{1733 2144 2145}. Calcium metabolism does not seem to be significantly affected²¹. The osteoporosis is believed to result from a primary protein loss of the bone matrix.

Hypertension; Renal and Ocular Involvement

The outstanding cardiovascular complication of the classical Cushing's syndrome and of related hyperadrenocortical conditions is arterial hypertension which, although varying between moderate and extreme degrees, is present^{1127 2147} in most instances, even in infants and young children^{1148 2149 2150 2151 2152}. Both the systolic and the diastolic pressure tend to be elevated and save for an occasional case with lively fluctuations²¹⁵³, they remain on fairly steady levels. Paroxysms, like those in patients with tumors of the adrenal medulla, do not occur. Taken all in all . . .

... conditions which are commonly encountered in pheochromocytomatous and essential hypertension.

In a series of 25 cases of Cushing's syndrome, all of which had basophil adenomata²¹⁵⁷, hypertension was present in 90 per cent, in one instance as high as 300 mm systolic and 180 mm diastolic, while one patient, whose adrenals seemed to be normal, had a pressure of only 95/50 preceding her

and polydipsia occur in some isolated cases. Laboratory examinations reveal in many instances a polycythemia, lymphopenia, low eosinophil count, insulin-resistant hyperglycemia and glycosuria, moderate deviations of the basal metabolism rate above or below the zero line, and a mild albuminuria.

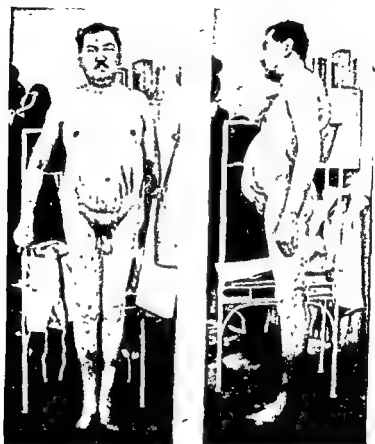


FIG. 13 One of the three which H. Cushing's interpreted by H. Cushing. Bull. Arch. intern. Med. 7: 443, 19

Cushing's syndrome of basophil adenoma upon basis based (Repro- W Raab, Wien 1910)

In the presence of adrenal carcinoma, the clinical picture is complicated by signs attributable to the malignant character of the tumor

Electrolytes

Abnormalities of the electrolyte metabolism occurring in Cushing's syndrome are chiefly characterized by an almost invariably demonstrable diminution of serum potassium^{53 542 1420 2164 3642} and a somewhat less consistent augmentation of serum sodium^{1192 1420 2164}. In one case, these changes were seen to return to normal after partial adrenalectomy¹⁴²⁰. The fact that one investigator²⁰⁶⁹ failed to discover any significant deviations of the serum



FIG. 14. Effect of desoxycorticosterone acetate (DCA) upon size of the heart in a normal young male. A, before DCA; B, after 5 daily injections of 20 mg DCA; and C, one week later (After W. Hanh, *Am Heart J.* 24:365, 1912).

death from septicemia. Normal or at least not conspicuously abnormal adrenal glands were found in 20 per cent of the hypertensive cases. The others were described as hyperplastic or as containing abnormally large quantities of lipids; one was carcinomatous. Renal abnormalities were present without exception in all 20 cases in which data concerning the kidneys were recorded. In two of these cases, the diagnosis "malignant nephritis" and "malignant nephrosclerosis" respectively was made. Both had elevated blood urea values but full-fledged uremia seems to be a comparatively uncommon event in Cushing's syndrome. Hypercholesterolemia was a frequent but not regular finding.

Ocular vascular lesions have been observed in many cases^{1060, 1753, 2190, 2933}. They were of the same nature as those occurring in essential hypertension and in malignant nephrosclerosis and may progress from slight changes to severe neuroretinitis³⁶⁵¹.

Cardiac Manifestations

The cardiac involvement in hyperadrenocorticism is less dramatic but in the end perhaps even more disastrous than in the pheochromocytoma syndrome. There is usually no history of palpitations. Accelerated heart action, whenever present, is only of a mild degree^{1420, 1973, 2212}. On the other hand, there develop almost always the typical signs of so-called "hypertensive" heart disease^{1400, 2542, 2492, 3187} and, unless the patient succumbs to an infection or other intercurrent illness, there is a greater likelihood for his death to occur from congestive heart failure than from other forms of ultimately fatal cardiovascular disturbances, such as uremic heart failure^{273, 634, 2451} or cerebral vascular accidents^{2190, 2367, 2905}.

In this connection, it may be said that temporary cardiac enlargement has been produced in humans by the writer by means of over-dosage of DCA, before any elevation of the blood pressure level and increase of serum sodium concentration had taken place (Fig 14)^{2663, 2704}. In some of these cases, the electrocardiogram showed flattening or inversion of the T-wave for periods as long as four weeks after discontinuation of the drug²⁶⁶³ (Fig 15). Frank congestive heart failure with peripheral and pulmonary edema was elicited inadvertently in a number of patients with Addison's disease by over-treatment with DCA^{626, 969, 2129, 2135, 2190, 3390, 3646}.

Morphological Cardiovascular Lesions

Arteriosclerotic vascular lesions of a minor or major degree are found with great regularity at necropsy in cases of hyperadrenocorticism, even in young persons and children^{2370, 2477, 2657, 2592}. They concern both the aorta and other larger vessels, including coronary and cerebral arteries (lit., see²³⁹²), and may give rise to cerebral hemorrhages^{2367, 2905}, as e.g., in the case

the periarteritis nodosa pattern. The greatest similarity between experimental vascular changes, elicited by DCA, and those occurring in human hyperadrenocorticism, concerns the kidneys. In a series of 20 cases with Cushing's syndrome²⁵⁹², there was not one in which there were not noted some deviations from the normal, although they varied widely between simple congestion, "chronic nephritis" and severe "malignant nephrosclerosis".

Cardiac hypertrophy, especially of the ventricles, was likewise a constant phenomenon in 17 out of 19 patients with Cushing's syndrome²⁵⁹² and in other individually published cases^{2597 2542 2157 2531} (see Fig 61a)

Treatment

The therapeutic approach to the hyperadrenocortical syndrome, including its cardiovascular complications, presents greater difficulties and uncertainties than is the case with pheochromocytoma. The following questions should be taken into consideration when any therapeutic procedure is carried out: (1) Is there evidence for an adrenal tumor? (2) If so, are there any indications of atrophy and non-functioning of the other gland (ascertainable only during exploratory operation)? (3) If there is no tumor, can anything be achieved by conservative therapy or should surgery be

attempted, possibly combined with irradiation of the adrenal areas, may be tried as perhaps the most promising type of conservative treatment. Satisfactory and, in some cases, even spectacular results of this method have been obtained by a number of investigators^{189 845 1059 1192 1811 2012}, but, on the other hand, there are also reports of failures^{197 1148}, so that x-ray therapy cannot be relied upon with too much confidence.

The same seems to hold true for the administration of large doses of estrogens^{214 279 315 3215}, stilbestrol²²¹ and testosterone^{24 304}, despite remarkable improvements in a number of cases. Testosterone even if given orally has been shown to be effective in some cases.

Normotension, including the blood pressure, was achieved with parathyroid hormone treatment¹⁹⁵⁷

If the presence of a tumor has been ascertained, surgical removal is the method of choice, provided that the modern precautions against post-operative shock due to exhaustion of the remaining (often atrophic) gland and against possible chronic hypoadrenocorticism are taken. They are essentially the same as those described on p. 88 except that even greater emphasis must be placed on the administration of large doses of adrenal cortical extracts before and after operation^{171 180} and that catecholamine infusions are of lesser significance. In the post-operative period the dosage

of an eight-and-a-half-year-old boy²¹⁹⁰. These typical arteriosclerotic changes of the large vessels which, as a rule, display marked intima lipoidosis¹⁸¹⁵.

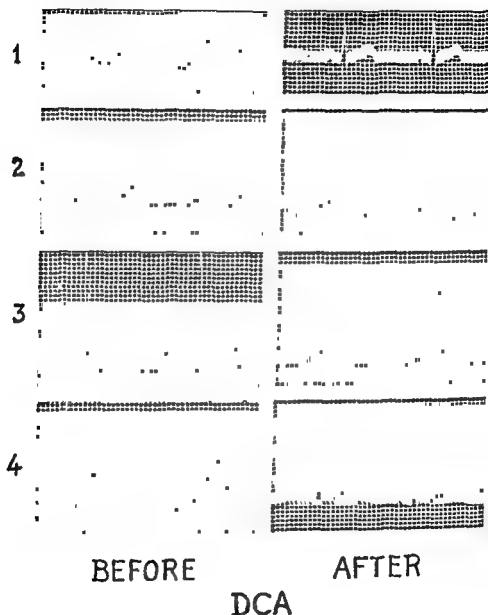


FIG. 15 Prolonged effect of desoxycorticosterone acetate (DCA) upon the electrocardiogram of a normal young male. Tracings taken before and four weeks after intramuscular injection of 50 mg. on three successive days (After W. Raab, *Am. Heart J.* 24: 365, 1942).

1759, 2136, 2892, cannot be considered as the direct human equivalent of the experimentally DCA-induced vascular lesions in animals because the latter are limited to the smaller arteries of the muscular type and resemble rather

cular symptoms after elimination of the tumor or partial bilateral resection of non-tumorous hyperplastic adrenal glands.

Taking the experimental facts discussed on p. 21, 28 and available clinical observations into account, the writer is inclined to interpret the mechanism of arterial hypertension in Cushing's syndrome and related states of hyperadrenocorticism in the following manner.

(a) Absolutely or relatively increased activity of adrenal mineralocorticoids alters the intracellular electrolyte pattern of the cardiovascular muscular tissue, by direct action upon the selective membrane permeability,^{1001 1002 1012} which leads to an excessive intracellular deposition of sodium^{854 1112 1120 1141}

(b) The resulting distortion of the gradient between extra- and intracellular electrolyte concentrations increases the electrical membrane potential of the vascular cells in such a fashion that the depolarizing action^{1001 1002 1012} of the ever present sympathomimetic catecholamines (epinephrine and nor-epinephrine from the supplying sympathetic fibers and from the adrenal medulla) will elicit exaggerated contractile responses^{1000 1001 1002}, i.e., hypertension. A potentiation of the pressor effects of epinephrine and nor-epinephrine has been demonstrated under the influence of DCA^{2006 2604 2761 2942}, and a weakening of the pressor effects of epinephrine, nor-epinephrine, DCA, and of their combination occurs during strict salt withdrawal²⁷²⁶ (Fig 16 and Fig 17a and b)

The above outlined concept ascribes to both the medullary and the cortical hormones a closely linked cooperative function in the mechanism of abnormal elevations of blood pressure, and, at the same time, it leaves ample room for several possibilities of quantitative mutual hormonal disproportions, which would produce identical pressor effects, such as an excess formation of sympathomimetic amines with about normal corticoids (e.g., in pheochromocytomas) or an excess formation of mineralocorticoids with about normal sympathomimetic amines (e.g., in Cushing's syndrome), or a theoretically thinkable combination of both in varying proportions (e.g., possibly in some cases of essential hypertension). It would likewise explain the complete disappearance of hypertension after removal of the offending over-active medullary and cortical tissue, respectively. Its implications regarding the problem of essential hypertension will be discussed on p. 263 ff., 281 ff.

The phenomena of cardiac hypertrophy, nephrosclerosis and generalized arteriosclerosis which are frequently seen in the presence of both pheochromocytoma and hyperadrenocorticism may also be considered on the basis of a mutually aggravating action of the adreno-sympathetic and adrenocortical systems and abnormally distributed hormone production: Epinephrine (from pheochromocytoma) would stimulate adrenal cortical

of cortical extracts must be diminished gradually and cautiously in order to avoid the risk of severe adrenal insufficiency in case the second gland should not have resumed adequate function.

While the mortality from the *removal of cortical tumors* was still about 40 per cent in 1934²⁵⁰¹, it fell to practically zero, according to a report published in 1949²⁵⁰⁰. The therapeutic results of the radical removal of benign *cortical neoplasms* can be described as excellent in most cases^{452, 1752, 2112, 2500}, including the cardiovascular status of the patients. In the presence of malignant tumors, the prognosis has to be viewed from a different angle, of course. With a recurrence of the tumor or the establishment of metastases, the clinical syndrome of hyperadrenocorticism may return¹⁷⁵¹.

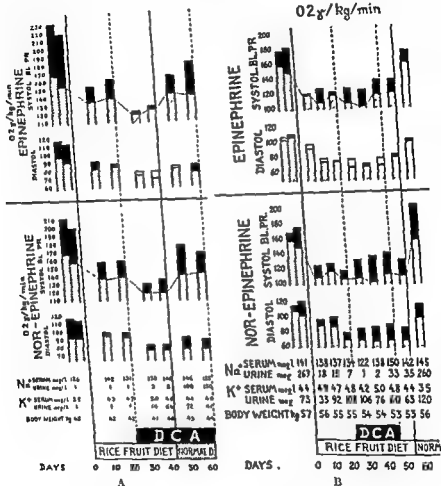
The most perplexing therapeutic problem is presented by those cases of Cushing's syndrome in which no tumor is found either by x-ray or by direct exploration. In one case, bilateral adrenal denervation¹⁷⁵⁹ was followed by complete disappearance of all symptoms, and also the hypertensive blood pressure returned to normal, an observation which throws an interesting light on the possibility of a neurohormonal involvement in the origin of hyperadrenocorticism, possibly by way of the epinephrine-pituitary-cortex detour (p. 45). Another method consists of bilateral subtotal adrenalectomy. It has been performed on five patients with Cushing's syndrome so far^{1751, 1865}, and resulted in the complete cure of two patients and in improvement of another case, while the two remaining patients died.

Heuristic Aspects of the Hyperadrenocortical Cardiovascular Syndrome

The cardiovascular manifestations, existing in cases of pheochromocytoma, and their disappearance after surgical removal of the hyperfunctioning medullary tissue, have been described on p. 78, as the results of a revealing experiment performed by Nature for the benefit of those interested in the pathogenic mechanism of arterial hypertension, hypertensive heart disease, arteriosclerosis and nephrosclerosis. The same can be said about analogous cardiovascular manifestations which are seen in connection with excessive adrenocortical function, tumorous or otherwise, and their disappearance after complete or partial surgical removal of the hyperfunctioning cortical tissue.

There is no doubt left concerning a decisive part played by some adrenocorticoids, notably the mineralocorticoids, in those cardiovascular syndromes whose hyperadrenocortical origin is made certain by (a) the presence of other typical hyperadrenocortical signs of the glucocorticoid-induced Cushing type and of androgen-induced virilization, (b) the presence of a cortical tumor or hyperplasia, (c) the disappearance of the cardiovas-

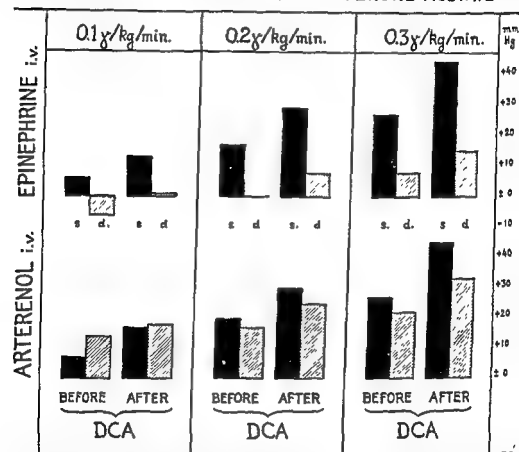
tomatous and of the hyperadrenocortical syndromes correspond to the specific functional characteristics of the two types of hormones which



are primarily responsible for the respective clinical states in the case of pheochromocytoma, there is a tendency toward acute cardiovascular episodes, in keeping with the fast-acting pharmacodynamic properties of epinephrine and nor-epinephrine

over-secretion via the pituitary and the adrenocorticotrophic hormone; desoxycorticosterone-like mineralocorticoids would potentiate the dynamic effects of epinephrine and nor-epinephrine upon the vascular walls (p 23)

VASOPRESSOR EFFECTS OF EPINEPHRINE AND ARTERENOL INTENSIFIED BY DESOXYCORTICOSTERONE ACETATE



AVERAGE BL.PR. BEFORE DCA: 136/81, AFTER DCA: 139/85
(DAILY 10 mg DCA DURING AVERAGE 17 DAYS. - 15 CASES)

FIG. 16 Potentiation of the pressor effects of intravenously infused mounting ment with desoxycorticosterone k areas represent average effects
(After W. Raab, R. J. Hum-
1397, 1950)

fl.). A participation of the pituitary growth hormone in the development of cardiac hypertrophy is suggested by the non-hypertensive hypertrophy of the heart in acromegaly (p. 167) and by experimental observations (p. 48)

Certain differences between the phenomenology of the pheochromocy-

evaluation of the role of cortical steroids in cardiovascular pathology as their counterpart, the hyperadrenocortical syndrome.

Endocrine Pathology

The two most extensive forms of chronic bilateral adrenocortical deficiency consist of (1) fibrocascous tuberculosis (in about 50-70 per cent of the cases¹²¹⁻¹²³, with an even higher incidence (85 per cent) in children¹²⁴), (2) atrophy or necrosis in almost all the remaining cases. The cause of the latter is usually obscure, except in the presence of a severe, supposedly primary, anatomical lesion of the anterior pituitary, which constitutes the central feature of Simmond's cachexia. While cortical atrophy in this latter syndrome may be reasonably attributed to a deficiency in the formation of adrenocorticotrophic hormone, there are increasing indications that atrophic changes of the adrenal cortex can likewise develop as an aftermath of infections and other stressful situations which may result in permanent functional exhaustion at either end of the pituitocortical axis¹²⁵⁻¹²⁹. The medulla of the adrenal glands is usually not involved in the destructive or atrophic processes¹³⁰⁻¹³². Concomitant atrophic changes of the anterior lobe of the pituitary are not infrequently seen¹³³ and in such cases it remains a matter of conjecture where the original derangement was located, unless a definite involvement of the gonads and thyroid, whose structure is less affected by cortical than by pituitary deficiency, manifests itself by distinct atrophy.

The classic syndrome of Addison's disease occurs somewhat more frequently in male individuals than in females (lit., see ¹⁴⁰) and its incidence is prevalingly concentrated in the age groups between 20-40 years. Children are less frequently affected, hardly ever before the tenth year¹². The disease is likewise very rare among the age groups past 60¹³¹.

Acute forms of severe adrenocortical insufficiency, due to sudden massive local hemorrhage, are a comparatively common event in children. If connected with overwhelming meningococcal septicemia (lit., see ¹⁴⁷), this usually rapidly fatal condition is designated as Waterhouse-Friedrichsen syndrome. Occasionally it may also be provoked by other bacteria, such as *Streptococcus hemolyticus* or *staphylococci*¹³⁴⁻¹³⁵.

Hormone Excretion and Assay

The *in vivo* tests of adrenal function, as far as concerned the excretion of the adrenal hormones, are of little value in view of the fact that their production is usually as profoundly affected by cortical destruction as that of the mineralo- and glucocorticoids, their urinary assay serves as a very useful diagnostic aid. In females, the 17-

By contrast, in the case of hyperadrenocorticism, acute hypertensive paroxysms are practically non-existent; the hypertension is generally a stable one, in accordance with the slowly developing effects of gradual alterations of electrolyte distribution in the tissues; anginal symptoms and sudden death are rare, owing to the absence of acute, violent adrenosympathogenic discharges, while congestive heart failure, which is connected with sodium retention, and death from this condition, constitute the usual final stage.

More will be said about the role of the adrenal corticoids in the origin and course of congestive cardiac failure on pp. 493, 499 and 513

Summary

Certain cardiovascular manifestations are attributable to the secretion of absolutely or relatively excessive amounts of mineralocorticoids by adrenal cortical tumors or hyperplastic adrenals, or they may be caused by a disturbance of the equilibrium between the mineralo- and glucocorticoid formation in favor of the former. They consist of a usually stable arterial hypertension, cardiac hypertrophy, chronic congestive heart failure, and arteriosclerotic-arteriolosclerotic vascular changes, especially in the kidneys.

All of these pathological conditions, with the exception of irreversibly established anatomic lesions, disappear completely after timely removal or reduction of the over- or dysfunctioning cortical tissue.

The striking clinical analogies between the pathogenic effects of adrenal medullary and mineralocorticoid over-activity on the cardiovascular system are believed to serve as an illuminating clue to the origin of some common functional and "degenerative" cardiovascular diseases, notably essential hypertension, "hypertensive" heart disease, nephrosclerosis and general arteriosclerosis. They illustrate the close, potentially pathogenic interrelationship between adreno-sympathetic neurohormonal and cortical hormonal functions.

An important link in this relationship seems to be the intracellular deposition of sodium under the membrane permeability-altering influence of the mineralocorticoids. There are indications that the resulting changes in the electrical potential of the membranes of the cardiovascular cells increase the contractile responsiveness of these muscular elements to adequate depolarizing stimuli, as exerted by the ever-present adrenergic neuro-hormones.

Hypoadrenocorticism (Addison's Disease)

Conditions of deficient adrenocortical function, in particular the full-fledged syndrome of Addison's disease, are of equal significance for the

General Symptomatology

The typical symptoms of Addison's disease, such as pigmentation of skin and mucous membranes, asthenia, digestive disturbances, loss of weight, and mental changes are so well known to most physicians and so extensively presented in recent monographs^{149, 212} that we do not need to describe them here in detail except for those which concern the cardiovascular system either directly or indirectly.

The severest acute complication of the syndrome, the so-called Addisonian crisis, which used to terminate the course of the disease until the advent of modern therapeutic procedures, is, as a rule, brought on by some stressful situation, even of a minor degree, such as a mild infection, trauma, exposure to unaccustomed temperature, emotional upset, etc., which is likely to exhaust the patient's last cortical reserves and to throw him more or less suddenly into a state of extreme hormonal deficiency. The critical stage is usually ushered in by aggravated weakness, epigastric pain with nausea, vomiting and diarrhea, and culminates in circulatory collapse, leading to coma with dehydration, hyperpyrexia, and ending in death, unless drastic measures are taken (see below).

During the chronic stage, the basal metabolism shows often a slight or moderate depression²¹³ as a result of a deficiency of cortical calorigenic action^{119, 204, 212}, but this is not a standing rule^{220, 244, 271}, except that low values are usually recorded when a crisis is approaching^{214, 217}. Otherwise, readings of -25 per cent or lower are strongly suggestive of concomitant hypothyroidism, either primary or as a partial feature of Simmond's disease²²⁷.

The profound disturbance of carbohydrate metabolism which exists in the majority of all cases of Addison's disease²²⁸, mainly due to a deficiency of the glucocorticoids, may or may not be distinctly reflected in a lowered blood sugar concentration (around 80 mg per cent^{223, 264}). The latter may reach critical hypoglycemia levels and this constitutes a particularly grave danger for the hypoadrenocortical patient, as it is apt to elicit a severe crisis. The glucose tolerance curve is usually flattened and may be followed by a perilous phase of hypoglycemia^{261, 271}. The abnormal sensitivity of patients with Addison's disease to insulin²⁷² calls for extremely cautious dosage of this hormone in the rare cases of combined Addison's disease and diabetes mellitus²¹⁵.

The presence of
adrenal

Milder cases of "hypoadrenia" due to congenital hypoplasia or a slight functional deficiency of the adrenal glands (infections, toxic influences, nutritional deficiency)^{119, 224} are often difficult to identify, even

ketosteroids may be found entirely lacking, while in males they may be reduced to the fraction which derives from the male gonads, i.e., near or below 5 mg per 24 hours^{1039, 2345, 2397}. A normal 17-ketosteroid excretion can be safely interpreted as ruling out Addison's disease²³⁹⁷. A temporary decrease of 17-ketosteroid excretion is often seen after infections, surgical interventions, etc., as a sign of cortical exhaustion¹⁰¹⁶.

The chemical^{290, 2347} and biological^{11017, 2462, 2464} determination of total corticoids and glucocorticoids respectively in the urine of patients with Addison's disease revealed abnormally low values in most cases. However, in some the readings were normal despite a low 17-ketosteroid excretion¹⁴³, which seems to indicate the occasional existence of diversities in quantitative cortical hormonal involvement.

In one case of Addison's disease in which the urine was tested for corticotrophic activity, the result was negative²⁰⁶⁶. The urinary excretion of sympathomimetic catecholamines was not found diminished in several cases¹¹⁹.

Thorn and co-workers²⁷⁵⁵ have introduced the simplest of all biological tests for the estimation of adrenocortical functional reserve, which is based upon the indirectly *eosinopenia-producing effect of injected epinephrine*. This effect is mediated by the epinephrine-induced liberation of the adrenocorticotrophic hormone from the pituitary anterior lobe²⁰³² which, in turn, stimulates the discharge of glucocorticoids from the adrenal cortex. These corticoids possess the specific ability to eliminate eosinophils from the blood in proportion to their own quantity. In normal persons, the subcutaneous injection of 0.3 mg of epinephrine is followed within four hours by a 49-80 (average 62) per cent diminution of the eosinophil count. In 11 patients with Addison's disease, it was found to be only 20-44 (average 21) per cent²⁷⁵⁵. Recant and co-workers²⁷⁵⁵ arrive at the conclusion that adrenocortical insufficiency can be practically ruled out if 0.3 cc epinephrine elicits a fall of the eosinophils of 50 per cent or more. The adrenal cortex seems to remain refractory to analogous stimuli for about eight hours after the epinephrine injection²⁷⁵⁵. In evaluating the results of the test, it should be kept in mind that a weak eosinopenic reaction to epinephrine, seemingly pathognomonic for cortical insufficiency, may be misleading in case of functional impairment of the anterior lobe of the pituitary. In such a case the pituitary will fail to respond with a discharge of ACTH and thus it will leave the adrenocortex more or less quiescent. Should there be any doubt about the validity of the epinephrine test, it is recommended to supplement it by the ACTH test²³⁹³ which acts upon the cortex directly and reveals the functional reserve of the latter. For the differentiation from panhypopituitarism, see p. 177.

dures, such as 17-ketosteroid assay, epinephrine- or ACTH-cosinopenia test, thermal sweat analysis, etc., are well suited to take their place.

The Robinson, Power and Kepler "water test"²²² makes use of the fact that the diuresis after ingestion of large amounts of water is inhibited in patients with hypoadrenocorticism.

It is clear that the disturbance in electrolyte distribution which is caused by a deficiency of adrenocortical function, will deeply affect various factors of water balance, particularly during a crisis. Loss of interstitial²²³ and plasma water²²³ occurs on account of (a) the excessive renal excretion of sodium which is accompanied by a roughly proportionate elimination of fluid, (b) the migration of water from the sodium-depleted interstitial spaces into the potassium loaded^{212 213 214} intracellular spaces as a feature of equilibration between extracellular and intracellular osmotic pressure²²⁴. Vomiting and diarrhea may further deplete the water stores of the body and thus precipitate an ultimately disastrous state of dehydration with a low circulating plasma volume²²⁵, hemoconcentration, renal insufficiency, azotemia and vasomotor collapse. The increased extracellular potassium concentration seems to contribute significantly to the phenomenon of muscular asthenia through its paralyzing effect upon striated muscle cells.²²⁶

Despite the undeniable importance of the primary anomalies of renal electrolyte and water excretion in adrenocortical insufficiency, regarding extra- and intracellular electrolyte distribution, one must not disregard the influence which a deficiency in cortical steroids seems to exert also directly upon the intracellular electrolyte pattern. Although only few details are known in this respect, there are increasing indications in favor of immediate hormonal effects upon the muscle cells and their electrolyte balance, independent of renal function and apparently playing a decisive role in the phenomena of muscular asthenia as well as arterial hypotension and myocardial weakness (see next section). It has been pointed out²²⁷ that both the classical manifestations of Addisonian crises²²⁸ on the one hand, and the full beneficial effect of administered corticoids on the other²²⁹ can develop in the presence of anuria and without extra sodium administration respectively, in other words, under conditions which preclude any influence of actual electrolyte loss or electrolyte replacement from outside the organism.

Some direct specific action of cortical steroids upon selective cell membrane permeability^{222 230} is suggested by findings concerning an increase of vascular and cellular membrane permeability after adrenalectomy and in Addison's disease^{231 232}. It could account, at least in part, for those intracellular electrolyte changes which, in the case of muscle cells, seem

with the entire armamentarium of the modern laboratory tests, including those concerning electrolyte metabolism (see below). Suspected patients must be watched carefully during any exposure to stress, as sudden catastrophic developments may occur. It is worthy of note that chemical changes have been observed in the adrenals of patients who had succumbed to various infections, namely a depletion of cholesterol, paralleled by an accumulation of phosphorus¹⁴².

Electrolytes

Disturbances of electrolyte metabolism form to a large extent the basis of the cardiovascular derangements which are characteristic of hypoadrenocorticism. Before considering this pathogenic factor, it should be emphasized that its manifestations cannot always be attributed entirely to an absolute deficiency of "mineralocorticoids". A disorganized interplay between the different types of corticoids whose influence upon electrolyte metabolism is, in part, of a mutually antagonistic character, may very well either exaggerate or conceal the effects of a diminished activity of the mineralocorticoids per se.

In discussions of the electrolyte situation in adrenocortical insufficiency, the main emphasis is often placed on renal sodium loss^{1394 2074 2339 2572} and retention of potassium²⁵⁷² with reference to experimental results, obtained in adrenalectomized animals, and to clinical findings¹³⁹⁶. An abnormal loss of sodium through the skin by means of thermal sweat has been likewise demonstrated in cases of Addison's disease⁴⁴⁹. In keeping with these observations, there exists in most instances of Addison's disease, though not without exceptions^{3157 2204}, a decrease of serum sodium²⁰⁷², especially when a crisis is impending or has developed³¹⁵⁷. The serum sodium may fall to levels as low as 111 mEq¹³⁶²³. The serum potassium level, on the other hand, tends to be elevated, but here, too, the findings may remain normal until the disease reaches an acutely critical stage³¹⁵⁷. In advanced cases, the ratio of sodium to potassium, which is normally about 30, is decreased³¹⁹⁷. Some investigators²⁵²⁷ doubt the dependence of the serum potassium concentration on cortical steroid activity and are inclined to ascribe it to variations of medullary epinephrine action instead.

Both sodium deprivation^{1396 2070 3644} and exaggerated potassium feeding⁶⁴⁰ aggravate the clinical picture of hypoadrenocorticism. Sodium restriction has even provoked fatal exacerbations^{1103 2029}. The diagnostic application of clinical tests, based on the specific reactions of Addison patients to sodium-poor or potassium-rich diets has fallen into disrepute because of the hazards connected with them. Their detailed description can be omitted therefore, especially because other more innocuous proce-

dures, such as 17-ketosteroid assay, epinephrine- or ACTH-eosinopenia test, thermal sweat analysis, etc., are well suited to take their place.

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Some direct specific action of cortical steroids upon selective cell membrane permeability^{131, 132} is suggested by findings concerning an increase of vascular and cellular membrane permeability after adrenalectomy and in Addison's disease^{133, 144}. It could account, at least in part, for those intracellular electrolyte changes which, in the case of muscle cells, seem

to contribute to the magnitude of electrical membrane potentials and thus to determine the contractile effect of depolarizing stimuli^{1000, 1001, 1002}, such as the action of epinephrine^{354, 326} which is weakened in patients with Addison's disease (see below). Alterations of the non-diffusible molecule concentration within the cells by adrenal insufficiency and by desoxycorticosterone respectively have also been considered as possible factors in the development of electrolyte changes in the tissues⁵⁵⁹.

Hypotension; Vascular Collapse; Renal Involvement

The most conspicuous cardiovascular anomaly in states of deficient adrenocortical activity is arterial hypotension with a low pulse pressure. In the great majority of patients with fully developed Addison's disease, the systolic pressure ranges between 80–110 mm Hg with a diastolic pressure below 70 mm Hg³¹³⁷. There are occasional exceptions, however, in which the blood pressure either remains more or less normal or descends into a seemingly normal range from preceding hypertensive levels^{903b, 1400, 2552}. With the development of a crisis, the blood pressure decreases further and may become entirely unidentifiable. There is usually a marked tendency toward postural hypotension^{509, 1125, 3371}, even in patients whose resting blood pressure level has not deviated far from normal or who have received otherwise adequate treatment³¹⁸⁷. Such episodes are accompanied by dizziness, blurring of vision, and faintness.

The fluctuations of the blood pressure which occur normally in connection with physical exercise, mental excitement, etc., are not entirely abolished in most cases²⁹³³, but the pressor response of patients with hypoadrenocorticism to injected epinephrine has been reported as being weakened^{47, 628, 2564, 3370, 3371} and the blood epinephrine concentration as being lowered⁴⁷⁹⁷. In adrenalectomized animals, the pressor effect of epinephrine²⁷⁷⁶ and nor-epinephrine has also been found diminished^{1040, 2733}.

As far as the causes of the behavior of arterial blood pressure in Addison's disease are concerned, it seems obvious that the extreme vascular collapse in a state of crisis is largely to be attributed to the drastic reduction of plasma volume and of circulating fluid. A negative water balance does not appear to be an absolute necessity for the development of hypoadrenocortical shock, however^{1293, 3335}, and the intrinsic derangement of electrolyte distribution must be held responsible in part. This applies to an even greater extent to the milder hypotension which prevails under more stable conditions and which can hardly be explained on the grounds of a reduced plasma volume alone, since the latter is frequently not demonstrable. Although it is possible to restore the blood pressure to normal levels by simply adding salt to the diet²⁰⁷¹, especially in patients with a low serum sodium concentration³¹⁸⁷, the response will be a much more intense one if

desoxycorticosterone is administered, even without additional sodium chloride. Indeed, desoxycorticosterone is capable of pushing the blood pressure up to outright hypertensive levels, something which cannot be achieved by the administration of salt per se.^{265, 272, 277} The suspicion of some workers that these pressor reactions to salt and to desoxycorticosterone might be due to a specific effect of ions upon vascular tone^{1004, 1005, 1011} seems to be indirectly supported by observations of the writer and his associates²⁴⁹. Withdrawal of sodium from the nutrition in humans was not only followed by a weakening of the pressor efficiency of the sympathomimetic amines, epinephrine and nor-epinephrine, which normally contribute to the maintenance of the blood pressure level, but also by diminution or disappearance of the normally demonstrable power of DCA to potentiate the pressor effects of those amines²⁶⁰ (Fig. 17, p. 103, Fig. 39, p. 287).

From the above enumerated findings, the tentative conclusion is drawn as a working hypothesis that the arterial hypotension in Addison's disease might be due to the following sequence of events: (1) a deficiency in mineralocorticoids leads to a derangement of intracellular electrolyte distribution in the cardiovascular muscular elements (depletion of sodium, accumulation of potassium), partly because of abnormal renal loss of sodium and retention of potassium, partly due to an alteration of cell membrane permeability and perhaps of non-diffusible molecule concentration within the cells, (2) the gradient between intra- and extracellular electrolyte concentration would then be altered in such a fashion that the electrical membrane potential is diminished which, in turn, would cause a diminution of the contractile response of the respective cardiovascular muscle cells to adequate intrinsic depolarizing stimuli¹⁰⁰¹, such as nor-epinephrine from the supplying sympathetic fibers or epinephrine, arriving via the blood stream (Fig. 39, p. 287). Weakness of the heart (see next section) must be considered as a contributing factor in the origin of hypoadrenocortical hypotension. Desoxycorticosterone is capable of remedying the hemodynamic anomalies of Addison's disease by replenishing or even exaggerating the depleted intracellular sodium stores so that the cardiovascular muscle cells will again be able to react to adequate intrinsic adrenosympathogenic stimuli with normal or even excessive pressor contractions. Salt alone does not suffice to create a hypertensive responsiveness of the vascular cells because the specific local action of desoxycorticosterone on the vascular cells seems to be a prerequisite for excessive intracellular deposition of sodium and for the resulting abnormally increased muscular contractility.

It is interesting to note that the hypertension-producing effect of DCA is considerably more pronounced in patients with Addison's disease than in normal individuals.²⁷⁷ This observation, together with the fact that other adrenal cortical extracts, although usually capable of normalizing

the blood pressure of patients with hypoadrenocorticism, do not produce hypertension and may even counteract the hypertensive effect of DCA^{257, 260}. This has been interpreted²¹⁸⁷ as indicating the existence of a functional equilibrium in the normal adrenal gland between the desoxycorticosterone-like potentially hypertension-producing compounds and other steroid fractions which would prevent excessive effects of the former. The deficiency or absence of antagonistic glucocorticoids which prevails in states of hypoadrenocorticism would then permit the artificially administered desoxycorticosterone, as a representative of the mineralocorticoid category, to display its full and unhampered hypertensive effectiveness.

On the other hand, it is suggested by experimental observations in animals^{1040, 2233} that the glucocorticoids are also instrumental in maintaining a normal contractile responsiveness of the vascular walls to nor-epinephrine (injected or discharged from the sympathetic nerve terminals) so that the hypotension of Addison's disease would seem to be attributable to a deficiency of both mineralo- and glucocorticoids.

Kidney function is normal in the quiescent stage of the disease, according to crude clinical tests^{1400, 2157}, but more detailed studies²²⁴⁵ reveal a distinct impairment of tubular reabsorption. These findings are paralleled by experiments in adrenalectomized animals¹³⁴² which suggest an inability of the tubules to reabsorb sodium, combined with a deficient potassium clearance. The abnormalities mentioned proved reversible, at least to some extent, by treatment with DCA²²⁴⁵ or cortical extracts^{1332, 2157}. The rather severe renal excretory impairment which supervenes during Addisonian crises and which is accompanied by azotemia, must be considered as a secondary complication, caused by dehydration and shock^{2220, 2224}, rather than as a specific feature of hypoadrenocorticism²¹⁸⁷.

Cardiac Manifestations

Subjective symptoms of cardiac origin are not a prominent feature in Addison's disease. Dyspnea and palpitations, although often occurring in connection with the slightest physical exertion, do not constitute very much of a problem in these patients because of the automatic limitation of their physical activity which is forced upon them by their general weakness and muscular asthenia. On physical examination, the heart sounds may appear weak and indistinct^{1400, 2298}. Orthostatic hypotension is frequently accompanied by marked tachycardia¹⁴⁰⁰ as a result of poor filling of the heart. On the other hand, the appearance of bradycardia may foretell an approaching crisis²¹⁵⁷. This latter phenomenon has been interpreted as being elicited by the rising serum potassium concentration²¹⁸⁷, but there are also patients whose heart rate increases during an aggravation of their clinical status²¹. Signs of congestive heart failure, such as congestion of the liver, pulmonary

edema and venous engorgement, are non-existent in untreated Addison's disease. By contrast, hypoadrenocortical patients display a much more marked tendency to develop edema and other features of congestive failure, if treated with des-oxy-corticosterone, than is the case in normal individuals³⁴⁵⁻³⁵¹. This difference is believed to be due to a lack of DCA-antagonizing corticoids in hypoadrenocortical states¹¹³ and is paralleled by the finding of an exaggerated intracellular accumulation of sodium in the heart muscle of adrenalectomized animals under treatment with DCA³⁵².

The most constant objective evidence of cardiac involvement is the striking decrease of the heart size, as observed both by roentgenographic

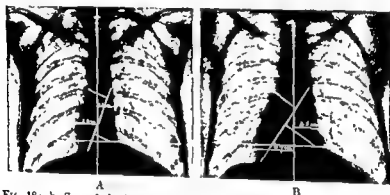


FIG. 18a, b Size of the heart of a patient with Addison's disease (a) during a crisis, (b) when "fully stabilized on synthetic cortical hormone". (After Th. H. McGavack, *Am Heart J* 21 1, 1941)

examination (Fig. 18a and b) and at necropsy^{146, 1221, 2124, 2407, 3231}. If the heart of a patient with hypoadrenocorticism appears normal in size, one must think of the possible concurrent presence of primary heart disease or hyperthyroidism³⁵⁷. During a crisis, the diminution of the cardiac silhouette shrinkage of the circulatory volume, reduced by its rapid disappearance when dehydration is corrected²¹²⁵. According to McGavack^{2126, 2128}, the average cardiothoracic ratio, i.e., the transverse diameter of the heart, divided by the transverse diameter of the thorax, is normally about 0.46, while values below 0.40 are usually found in cortical insufficiency, and 0.35 or less in Addisonian crises. The diagnostic reliability of this rule is somewhat reduced in persons with abnormally deep or flat chests²⁰⁰. As long as the individual patient serves as his own control, however, the measurement of the cardiac silhouette and, to a lesser extent, the calculation of the heart volume in relation

to body surface²¹³⁶, are useful in following the clinical course of the patient and especially in evaluating the results of therapy. Treatment with adrenal cortical extract or DCA restores the normal size of the heart^{2122, 2136, 2138}, whereas the administration of salt and water alone does not seem to achieve this effect, even when the circulatory volume is brought back to normal²¹³⁶. This behavior has been held against the concept that the reduction of the heart size in Addison's disease be attributable in its entirety to the reduction of blood volume, also in the quiescent state, when no crisis is impending. Under-nutrition as the cause of diminished heart size can also be ruled out in all probability, as it does not produce the profound alteration of the heart weight to body weight ratio which is a characteristic of Addison's disease^{2136, 2150}. Another fact which speaks in favor of a direct specific action of adrenal corticoids, especially of the mineralocorticoids, upon the trophic state of the myocardium, is the ease with which a pathological enlargement of the heart can be provoked in hypoadrenocortical patients by an over-dosage of DCA^{269, 2136, 2139}. Slight to moderate cardiac enlargements were also observed in normal individuals after administration of DCA, even before the blood pressure level and the serum sodium concentration had begun to show any significant increase^{266, 2704}.

Although the *electrocardiogram* may remain perfectly normal in about 50 per cent of the cases of Addison's disease^{21, 2200, 2227}, there are numerous observations of pathological changes on record. They consist chiefly of low voltage^{21, 247, 2223, 2187, 2200}, prolonged P-R and Q-T intervals^{247, 2200} and flattening or inversion of the T-waves^{21, 247, 215, 2204, 2187}. These latter changes, occurring in about one-third of the cases²²⁰⁰, and depressions of the S-T segment²²⁰⁰ are most likely to appear during a crisis and coma²¹, but even in these grave conditions, the electrocardiogram may remain normal^{21, 2200}. Conduction disturbances^{215, 2223} and arrhythmias occur only rarely.

Nothing definite is known about the myocardial metabolic changes, underlying the electrocardiographic manifestations of hypoadrenocorticism. From animal experiments it was concluded that the elevation of serum potassium^{2519, 2654} and of intramyocardial potassium⁶⁶⁵ might be responsible for some of the electrocardiographic abnormalities observed. However, the potassium concentrations in the serum of human Addison cases do not rise as high as those found in adrenalectomized animals²¹⁸⁷ and among the electrocardiographic manifestations, occurring in humans, only an occasional elevation of T²²⁷⁶ is consistent with potassium effects. The more common changes mentioned above belong rather in the category of the so-called "anoxia" pattern. A tentative explanation for this fact was offered on p. 30, where other metabolic peculiarities of the hypoadrenocortical heart are also listed. The irregularity of the findings was ascribed²²⁰⁰ to the composite interference of various factors, such as deficiency of gluco-

corticoids, electrolyte imbalance, changes in extracellular fluid volume, anatomical lesions of the heart muscle, etc. The not infrequent presence of fibrinous pericarditis^{226a} may be an additional factor, contributing to electrocardiographic alterations.

Normalizations of the electrocardiographic changes in Addison's disease have been achieved by administration of cortical extracts²¹ and cortisone^{226b}, but treatment with DCA led to a worsening rather than to an improvement of the electrocardiogram^{82a, 226c, 226d}, probably in accordance with the damage which is being inflicted upon the heart by the slightest over-dosage of this steroid and by the accompanying loss of potassium^{100b} plus deposition of sodium in the myocardial cells^{94a, 226e}. By the same token, full-fledged congestive cardiac failure with pulmonary and peripheral edema is a common and dreaded complication of injudicious DCA dosage, which has even resulted in death in some cases in the early days of desoxycorticosterone therapy when its hazards were not yet sufficiently appreciated^{94g}.

Morphological Cardiovascular Lesions

Arteriosclerotic lesions, if ever found at necropsy in patients with Addison's disease, can be assumed to have developed before the function of the adrenal cortices had become impaired. In a report on the pathology

of the aorta at the valve and in the ascending part was roughly proportional to the weight of the hearts (see below). However, cerebral vascular lesions were observed in a case in which death had been induced by over-treatment with DCA¹⁰⁷. In another series of 24 cases²⁵⁷ there was no

hypertensive before renal arteriosclerosis patients are general

They showed in a relatively high percentage (about 20 per cent) congestion and in approximately 30 per cent tubular atrophy with flattening of the epithelial cells and intertubular edema¹¹⁶. These alterations have been ascribed to the influence of low blood pressure and lack of oxygen¹¹⁶.

The heart weight was found to be less than the normal average in the majority of autopsied cases^{106, 248}. The myocardium appears flabby. Diffuse areas of degenerated muscle fibers have frequently been seen in the hearts of both untreated and treated patients with Addison's disease^{217, 226f}. The heart of a patient who had succumbed to cardiac failure, caused by over-dosage of DCA, showed widespread myocardial necrosis^{120g} of the DCA-induced type²⁴⁶.

Treatment

In comparison with the hopeless fatalism which characterized the therapeutic attitude towards Addison's disease throughout the first quarter of this century, the situation has completely changed since the production of potent adrenal cortical extracts by Rogoff and Stewart²⁵²³, Hartman²⁴⁰², and Pfiffner and Swingle²⁵⁴³ (1927-1929), the recognition of the clinical value of sodium intake by Loeb²⁰⁷⁰ and of potassium restriction by Wilder²⁶¹⁹ (1933-1936), and the discovery of desoxycorticosterone by Reichstein²⁷⁶¹ (1938).

In recent years, the originally prohibitive cost of hormone therapy has been reduced to such an extent that the treatment by administration of 10-15 grams of extra salt alone or in combination with reduced potassium intake, has lost much of its clinical importance. Indeed, the powerful sodium-retaining effect of DCA and the danger of a toxic over-loading of the cardiovascular tissues with sodium under the influence of this steroid, make it necessary that special care be taken not to exceed a certain amount of salt in the diet if the patient is being treated with DCA. On the other hand, potassium is freely excreted during DCA administration and a deliberate restriction of the alimentary potassium intake under these circumstances might do more harm than good by precipitating the development of a critical hypopotassemia with muscular weakness and paralysis³¹⁹¹.

In general, it can be said that in most cases of Addison's disease satisfactory therapeutic results are achieved by *DCA, combined with a proportionate intake of sodium chloride*, as long as no complications intervene which are apt to provoke a crisis. Among the various techniques of DCA administration, the sublingual route^{32 3134} is uneconomical and rather irregular in its effectiveness^{3157 3190}, daily intramuscular injections in oil involve obvious inconveniences and thus preference is usually given to the subcutaneous implantation of pellets of the crystalline steroid³¹⁰³, except in very mild cases which do not require daily injections and in elderly patients, because the latter are more likely to develop cardiovascular complications³¹⁵⁷. Before pellets are implanted, the patient should be kept under observation for two to three months with injection therapy in order to determine his minimal daily DCA requirement, which varies between 1.5 and 5.0 mg³¹⁵⁸ in conjunction with salt intake. Using the effect of DCA upon the size of the heart (p. 116) as a criterion²¹³⁶, McGavack has devised a formula according to which the daily dose of DCA in milligrams, multiplied with the daily ingested sodium (not sodium chloride) in grams, should give a figure somewhere between 30 and 45. However, in some cases, the increase in heart size lags behind the rise of the blood pressure, and hypertensive levels may be reached without a concomitant enlargement of the heart silhouette beyond normal²¹³⁵. In untreated cases, the DCA require-

ment is usually greater in the beginning than the daily maintenance dose which is necessary to keep an adequate electrolyte balance over longer periods of time. In a series of 100 cases, the average number of implanted pellets of 125 mg each was four for males and three for females³¹⁷. It was determined in proportion to their specific rate of absorption and to the patient's daily injection requirement, after the latter had been well established. The efficacy of the pellets lasts from 10-13 months³¹⁷. Its decline can be judged from the behavior of the blood pressure, the diameter of the heart, and the subjective sense of well-being of the patient. To some extent, the fluctuations in the patient's condition can be compensated by additional salt intake. Supplemented by a high caloric diet, the DCA-sodium therapy was found adequate for rehabilitation of more than one-half of Thorn's 200 patients³¹⁷.

Despite its outstanding therapeutic value, DCA cannot be considered as offering full functional substitution for total adrenal cortical deficiency. It represents only the group of mineralocorticoids and hence is unsuited to correct the derangements of carbohydrate, protein, and fat metabolism, which are due to the lack of glucocorticoids. While of lesser significance during the "intercritical" periods, these metabolic disturbances come into prominence during acute states of stress, even of a mild degree (infections, surgery, gastrointestinal upsets, inadequate nutrition, etc.), and may cause their fatal outcome.

Complete hormonal substitutive treatment becomes imperative under such circumstances as well as in the case of critical hypoglycemia and general weakness. This can be achieved by the parenteral administration of whole adrenal extracts, either aqueous or in oil. In case of a fully developed crisis, 25-50 cc of aqueous cortical extract must be applied intravenously at once, plus an equal amount subcutaneously, combined with 10-20 mg of DCA intramuscularly. (The intravenously injectable desoxycorticosterone glucoide (DCG) is less effective^{311, 125}.) Additional smaller doses of cortical extract, up to a total of at least 100 cc, and 10 more milligrams of DCA should be administered during the first 24 hours, after which the dosage can be gradually diminished over a period of several days, in accordance with the patient's reaction³¹⁷. The hormone treatment must be accompanied by ample infusions (2-3 liters) of saline and glucose solutions and by maintenance of a comfortably warm outside temperature. Salt and fluids can and should be employed more liberally in hitherto untreated patients in whom a crisis has developed, as compared with those who are under the influence of pre-treatment with DCA and relatively well hydrated. Patients of the latter kind must be watched with particular care for the formation of edema which is predictable from a rapid increase in weight, and pulmonary congestion³¹⁷.

If the preparations made from natural adrenal cortical material were less expensive, they would constitute the ideal therapeutic agents for hypoadrenocorticism because they cover the entire range of cortical activity, including sodium retention and deposition, while being practically devoid of the toxic potentialities inherent in the synthetic DCA. Under present conditions, however, their use must remain limited largely to the above named emergencies. Cortisone in maintenance doses of 15 to 30 mg per day or in the form of implanted pellets (1.0 gm) which last for three to four months, in combination with DCA or salt, proved very effective in the treatment of Addison's disease²¹⁹⁶.

As already mentioned on pp. 113 and 115, over-dosage with DCA, especially if coinciding with the ingestion of too much salt, is prone to give rise to arterial hypertension^{2129 2191} and to the most dangerous complication of this form of therapy: congestive heart failure with cardiac enlargement and associated with peripheral and pulmonary edema^{209, 259, 2129 2135 2190 2334 3391 3615}. Such a turn for the worse is likely to end in death, unless sodium or DCA or both are immediately reduced. Some of the implanted pellets may have to be removed surgically. Bed rest, digitalis, mercurial diuretics, and ammonium chloride are additional requirements.

Apart from the subacutely fatal form of cardiac failure, sudden, unexpected death may likewise occur as a result of DCA treatment²¹³⁷. Whether the potentiation of cardiovascular reactions to the adrenosympathetic catecholamines through DCA^{2663, 2704} is involved in this mechanism cannot be decided at present.

ACTH is ineffective in Addison's disease²¹⁹⁶.

Heuristic Aspects of the Hypoadrenocortical Cardiovascular Syndrome

The cardiovascular manifestations of Addison's disease may be regarded as the third in the series of Nature's experiments concerning the problems of hormonal cardiovascular pathology. In this instance, however, artificial experimentation (adrenalectomy) has more successfully competed with spontaneous "experimentation" than had been the case concerning adrenal medullary and cortical over-function.

The salient cardiovascular features of hypoadrenocorticism consist of arterial hypotension and cardiac atrophy, plus a conspicuous absence of arteriosclerotic vascular lesions. The direct contrariness of these peculiarities to the cardiovascular anomalies, existing in hyperadrenocortical syndromes (hypertension, cardiac hypertrophy, arteriosclerosis) is further emphasized by the extraordinary facility with which hypertension and cardiac enlargement can be elicited in Addison patients through a therapeutic over-dosage of the synthetic mineralocorticoid desoxycorticosterone. This latter fact has also been pointed out as indicating the importance of

a proper balance between mineralo- and antagonistic glucocorticoids in the normal protection of the cardiovascular system against hormonal injury.

In view of the apparent role of intra- extracellular electrolyte distribution and resulting electrical membrane potential changes (p. 25) in cardiovascular muscular contractile responsiveness to adrenosympathetic neurohormonal depolarizing stimuli, the phenomenon of hypoadrenocortical arterial hypotension appears a logical consequence (Fig. 39, p. 257). It will also serve as a valuable help in the interpretation of the hormonal basis of other forms of depressions of cardiovascular tonus (p. 178, 328, 331). The absence of arterio-sclerosis and the presence of cardiac atrophy in patients with Addison's disease in conjunction with their opposite counterparts in the hyperadrenocortical syndrome will be later incorporated in deliberations concerning the pathogenesis of arterio-sclerosis, of "hypertensive" heart disease, and of "idiopathic" cardiac hypertrophy.

Summary

In Addison's disease and related states of hypoadrenocorticism, an involvement of the cardiovascular system is manifested by arterial hypotension, including the orthostatic type, and cardiac atrophy with occasional degenerative changes which, however, are qualitatively different from those seen in hyperadrenocortical syndromes. Arterio-sclerosis is conspicuously absent. Hypotension reaches extreme degrees during Addisonian crises and the size of the heart is then even further reduced, probably because of maximal diminution of the circulatory volume.

All hypoadrenocortical cardiovascular anomalies can be corrected by substitutive therapy with adrenal cortical extracts or DCA. While the former are practically non-toxic, an over-dosage of the latter is likely to produce arterial hypertension and cardiac enlargement, eventually resulting in congestive heart failure and even death, probably in part because of a lack of counterbalancing glucocorticoids. Such complications occur especially if too much sodium is ingested during the treatment. In states of crisis, whole adrenal extracts or cortisone, salt and glucose must be administered alongside with DCA.

The disturbances of electrolyte balance in Addison's disease (loss of sodium, retention of potassium) seem to be largely responsible for the cardiovascular manifestations in which a diminished or abolished contractile response of the sodium-depleted, potassium-loaded cardiovascular muscular elements to the physiologic adrenosympathogenic neurohormonal depolarizing stimuli appears to be a prominent factor.

There is some reason to believe that a deficiency of glucocorticoids is likewise instrumental in decreasing the blood pressure by interfering with the vascular responsiveness to nor-adrenaline, liberated at the sympathetic nerve terminals in the vascular walls.

Thyroid

Hyperthyroidism (Thyrotoxicosis)

Endocrine Pathology

The morphological changes which characterize a hyperfunctioning thyroid gland, either of the diffuse parenchymatous or adenomatous type, consist chiefly of a marked increase of epithelial cells, irregularity in form and size of the acini, lack of colloid, and lymphoid infiltration. The origin of these anomalies and of the clinical syndrome connected with them is still obscure in the great majority of cases. The histological resemblance of hyperfunctioning human thyroid glands to those of animals, treated with the thyroid-stimulating hormone (TSH) of the anterior pituitary lobe, appears suggestive of a primary exaggerated elaboration of TSH as the pathogenic basis for at least a substantial group of cases²⁷⁵⁴.

In morbid states of the thyroid which concern this gland primarily, such as thyroiditis and malignancy of the thyroid, clinical signs of hyperfunction are rare. In a few patients^{415 2275 3067} in whom total ablation of a carcinomatous thyroid had been carried out, thyrotoxic signs developed subsequently in the presence of metastases which had assumed hypersecretory characteristics, presumably as a result of an uninhibited release of TSH from the pituitary which is otherwise kept under control by the normally functioning thyroid gland.

Aside from the rather nebulous "constitutional predisposition" for hyperthyroidism, there are some specific etiological factors with hypothalamic-hypophyseal implications³⁰⁰⁶, for which at least a definite time relationship with the onset of symptoms can be claimed: (a) acute intensive emotional excitement^{167 1134}, (b) CO intoxication^{105, 2650, 3453}; (c) encephalitis^{2492 2623, 2400, 2474 3324}; (d) acute infections²²⁷⁵, (e) puberty, pregnancy, and menopause²⁷⁷⁵.

The most important known single etiological agent, capable of provoking the thyrotoxic syndrome, is iodine, especially if ingested in the form of inorganic compounds, such as potassium iodide^{352 1402 2656}. The resulting "Jod-Basedow", as it is called in the Alpine regions of Europe, where it constitutes the majority of vast numbers of cases of hyperthyroidism, is almost unknown in North America, except as a complication in patients with adenomatous thyroids who had been treated with iodine³⁰². In view of the familiar therapeutic efficacy of iodine administration in existing thyrotoxicosis, the mechanism of this paradoxical phenomenon is difficult to understand. As it occurs mainly in geographical areas with a low iodine

content of soil, water and food and a high incidence of goiters, it may be comparable to the severe toxic effects, produced by otherwise innocuous doses of potassium iodide, in animals with "cabbage goiter"²²², possibly through the synthesis of excessive amounts of thyroxin from the ingested iodine with the accumulated iodine-free thyroxin precursor thyronin¹. In the United States, there does not seem to exist any clear-cut coincidence between the geographical distribution of goiter and thyrotoxicosis.

Hyperthyroidism may occur in all age categories, but it appears most frequently in the third and fourth decade. In children it is seen very rarely. The sex incidence shows a distinct preponderance of the female sex in a proportion of about 4:1²²³ with the exception of certain goiter areas, where the proportion between females and males was found to be about 4:3²²⁴.

The development of thyrotoxic symptoms as a result of injudicious medication with thyroid preparations, the so-called "thyrotoxicosis factitia", is less common in America than in Europe but has been observed in a number of cases also in this country^{225, 226, 227}.

Hormone Production and Secretion

By means of studies with radioactive isotopes, it has been shown that elementary iodine, which reaches the thyroid with the blood stream as iodide, is trapped by the gland. Through an enzymatic process, it is oxidized there to elementary iodine. In the parenchymatous cells or also within the colloid stores of the follicles, iodination of tyrosine radicals to diiodotyrosine takes place, which is followed by coupling of two diiodotyrosine molecules to thyroxin, and by a compound formation of the latter with protein (colloid) to thyroglobulin, which is the storage form of the hormone²²⁷⁻²²⁹. Delivery of the active material into the general circulation seems to be initiated by an enzyme-induced break-down of thyroglobulin into soluble thyroxin-polypeptide compounds²³⁰. The latter are absorbed from the blood by various tissues in which they could be traced by the radioiodine technique. The highest concentrations seem to occur in the liver, followed by skeleton muscles and the heart muscle. After local decomposition of the hormone, iodide re-enters the circulation and the cycle begins anew²³¹.

Contrary to older views, the secretory activity of the thyroid gland is no longer believed to be directly regulated by nervous pathways but to be entirely governed by the specific humoral influence of the thyrotrophic hormone (TSH) of the pituitary¹⁰⁸. The action of the latter manifests itself by a rapid increase of intracellular colloid droplets which has been used as a criterion for biological TSH assay^{232, 233}. The release of hormone from the thyroid of the entire gland²³⁴. In this

thyroid parenchyma²⁷⁵. The secretion of TSH by the pituitary is being kept within bounds through a retrograde inhibitive influence of the thyroid hormone, while on the other hand it seems to be subject to central nervous stimuli from the hypothalamus²⁷⁵.

Considering the above-outlined interplay of functions, it is not surprising that the concentration in the blood³⁶⁴ and the urinary excretion of TSH in hyperthyroid states has not been found increased¹⁴³.

The general metabolism-stimulating activity of the thyroid hormone makes it almost certain that it must exert some effect on every single part of the endocrine system. However, these effects seem to be of such a subtle nature that only little has been reported up to the present regarding secondary functional changes in other endocrine glands in cases of thyrotoxicosis. As far as the adrenals are concerned, a certain degree of degeneration and atrophy of the cortex has been seen in such individuals¹⁴⁰ which may be ascribed to the chronic "stress" of exaggerated thyroid function and resulting adrenal cortical exhaustion, but cortical hyperplasia has also been observed occasionally¹³³. Functional tests suggest a decreased adrenal cortical reserve in severe cases of hyperthyroidism, apparently as a result of prolonged over-stimulation⁶⁶. The excretion of water-soluble corticoids in the urine was found higher than normal in 7 patients³³⁷.

Of particular interest for the problem of thyroid interference in the cardiovascular system is the intensifying action of the thyroid hormone on adrenosympathetic neurohormonal cardiovascular effects¹⁴¹. It will be discussed more in detail on p. 144 ff. The concentration of sympathomimetic catecholamines in the blood of thyrotoxic patients was found within normal limits²⁶⁷.

General Symptomatology; Diagnosis

The components of the clinical picture of hyperthyroidism, which was originally described by Parry in England (1786), Flajani in Italy (1802), Graves in England (1835) and Basedow in Germany (1840), are manifold and there hardly exists a patient who would display all of those signs which are considered as typical. Some phenomena occur with greater regularity, others are seen less frequently; even each one of the "classical" signs may be missing. It will suffice here simply to enumerate the most characteristic thyrotoxic manifestations, as far as they have no immediate bearing on cardiovascular pathology. (1) diffuse enlargement of the thyroid or *nodular goiter, sometimes visible or palpable only when the patient swallows*, occasionally a *bruit and thrill over the gland*, (2) *wide palpebral aperture with staring, apprehensive expression*, in a minority of cases *exophthalmos*; (3) *tears appearing in the eyes on slightest emotional provocation*, especially in women, (4) *flushing of face, neck, and*

upper part of chest in women; (5) moist, shiny skin; often profuse, warm perspiration; (6) thin, silky hair with a history of unusual loss of hair on combing; (7) fine tremor of outstretched hands, tongue, and closed eyelids; (8) motor restlessness, constant fumbling with fingers, (9) weight loss, usually accompanied by good appetite; (10) muscular asthenia which may progress to the full-blown syndrome of myasthenia gravis¹⁰⁶, marked fatigue, (11) over-sensitivity to warm temperature; (12) occasionally intense diarrheas, but in many other cases constipation; (13) oligo- or amenorrhea, (14) mental excitability, anxiety, quarrelsomeness, changing moods, sometimes outright psychoses.

Among laboratory tests for thyrotoxicosis, the determination of the basal metabolic rate (BMR) is being used almost invariably. Abnormal elevations from at least plus 10 per cent up to plus 100 per cent and more can be interpreted as being consistent with the diagnosis, provided that no technical errors are involved. Escape of air through the nostrils, through a perforated eardrum, or between lips and mouthpiece will yield false

enough tension to distort the results and the test should be repeated in such cases. However, even technically correct high readings per se do not prove the presence of hyperthyroidism. Other conditions connected with an elevated basal metabolism are: essential hypertension^{136, 221, 414, 1361, 1419, 1508, 2359, 2463}, malignant hypertension²⁴⁵², congestive heart failure^{1515, 2347, 2790, 3192}, coarctation of the aorta²¹⁶⁸, beri-beri²⁴⁷¹, leukemia¹²³⁰, multiple myeloma¹¹⁴⁴, polycythemia²³⁰¹, pregnancy^{2530, 2823}, pheochromocytoma (p 75), and several more⁴⁰².

In occasional cases, the BMR values appear less elevated than one would expect from the patient's general clinical status¹⁵⁶⁷. This can be due to the fact that the "normal" basal metabolic level of some persons is unusually low. (The writer has seen BMR readings of -15 per cent to -20 per cent in perfectly healthy individuals.) It is clear that in patients of this type a BMR of +20 to +30 per cent is not

with t
to be,

In interpreting the results of BMR determinations, one should always keep in mind that thyroid function is only one out of a number of factors which are responsible for total oxygen consumption. The outstanding calorogenic effectiveness of the sympathomimetic catecholamines (as exemplified by the excessive hypermetabolism of pheochromocytoma cases) and the potentiating action which the thyroid hormone exerts upon some of their cardiovascular functions (p 34, 35), suggest even the possibility

that the calorogenic effect of the thyroid hormone might be mediated in the tissues through these ubiquitous amines, in conjunction with adrenal cortical activity^{1193, 2906, 3112}. Certain experimental observations^{150, 722, 2221, 2964} are in agreement with this view, which is also supported by the abnormal resistance to thyroxin of sympathectomized animals⁵⁸¹, the inhibition of the effect of thyroxin upon general oxidations by sympatholytic drugs¹⁴⁷, and the metabolic inefficiency of the thyroid hormone in adrenalectomized animals¹¹⁹³. The relation between muscular work, performed by thyrotoxic patients, and the accompanying increase of metabolism indicates an excessively wasteful oxygen consumption with abnormally low energetic efficiency^{741, 2612}, a characteristic which applies likewise to the action of the adrenosympathogenic neurohormones, especially on the heart (p. 11 ff).

Another metabolic peculiarity of thyrotoxic individuals which makes one think of a mediating adrenosympathogenic neurohormonal interference is the *lowered carbohydrate tolerance*: high blood sugar peaks with slow return after glucose ingestion^{719, 2275, 3696} and a tendency toward glycosuria²⁷²³.

Urinary creatine elimination is increased, while creatinine excretion and the creatinine index are diminished (lit., see ²²⁷⁵).

A slight or moderate depression of the blood cholesterol level is often quoted as a supposedly characteristic feature of thyrotoxicosis, but it does not occur regularly enough to be of definite diagnostic significance^{1016, 1612, 2142, 2645}.

On the other hand, the determination of protein-bound iodine in the serum might be considered as the most useful single laboratory test for the differential diagnosis of hyperthyroidism²⁷⁴² if its technical performance were less complicated and time-consuming. Normal values vary between 3.5 and 7.0 gamma per 100 cc. In thyrotoxic patients, they have been found elevated to levels of from 8 to 30 gamma per 100 cc^{630, 4502}. Misleadingly high readings may be obtained during weeks or months after exposure to iodine medication, cholecystography with iodine preparations, and the like²²⁷⁵.

A diminished urinary excretion of tracer doses of radioactive iodine indicates an increased absorption of ingested iodine by an over-active thyroid gland²¹¹⁶. Although the normal excretion values and those found in thyrotoxic patients overlap to some extent, a definitely low excretion will support the assumption of hyperthyroidism, while high values help to establish the differentiation from other conditions which are associated with a high BMR, by pointing toward one or the other of the latter²²⁷⁵. "Thyrotoxicosis factitia" can be distinguished from genuine hyperthyroidism by the normal or elevated excretion of radioiodine^{343, 2275}.

A more complicated but supposedly more dependable test is based on the

evaluation of the uptake and discharge of radioiodine by the thyroid gland by means of the Geiger-Müller counter²²⁶. The ingestion of 100 microcuries of I^{131} is preceded by the administration of 100 mg of 2-mercaptoimidazole and followed by 1 g of potassium thiocyanate as soon as the I^{131} -accumulation in the thyroid has reached its maximum. The disappearance of the radioactive material from the thyrotoxic gland takes place with greater rapidity than from the normal thyroid.

The simple calculation of I^{131} -uptake by the thyroid gland was not found sufficiently accurate for diagnostic purposes^{267a}.

In summing up, it should be stressed that the diagnosis of hyperthyroidism, while often obvious enough to be made at first glance even by the layman, may present a difficult problem in other cases. In these, only a careful scrutiny of details and an intelligently coordinated over-all evaluation of the patient's physical and mental status will lead to correct diagnostic conclusions. The role of the cardiovascular system in the clinical syndrome of thyrotoxicosis and in its diagnostic recognition will be discussed in the following sections.

The phenomenon of a so-called *thyrotoxic crisis* or *storm*, occurring after surgery or in connection with other stressful situations (infections,

... accumulation and coma, are so much like those seen in Addisonian crises that one may think of an acute state of adrenal cortical exhaustion, possibly enhanced by the thyroxine-potentiated epinephrine- Δ CTH-cortex mechanism. In fact, some evidence for a diminished functional cortical reserve in severe thyrotoxicosis has been presented⁶⁸³ and Means^{277b} has used adrenal cortical preparations in thyrotoxic crises with apparent success.

Blood Pressure and Pulse Pressure

For a long time, the behavior of the blood pressure in thyrotoxicosis was a favorite subject of statistical studies, since compilations of such data can be achieved with comparative ease and offer the guaranteed reward of publishable figures, regardless of their significance or lack of significance.

Due to the fact that in earlier reports emphasis was placed somewhat inconsistently on either the systolic pressure, the pulse pressure, or the mean arterial pressure, a good deal of confusion still exists in the minds of many physicians regarding the relationship between increased thyroid function and blood pressure.

Table 1 shows the results, obtained by several investigators^{11, 102, 277, 272, 170, 159, 210} in a total of more than 600 cases of hyperthyroidism, as far

as the systolic pressure is concerned, while findings regarding the pulse pressure are reported in Table 2. These data indicate (a) that a slight to moderate elevation of the systolic pressure occurs somewhat more frequently in thyrotoxic persons than in the corresponding age categories of non-thyrotoxic individuals, but that it cannot be considered a standing

TABLE 1
Systolic Blood Pressure in Hyperthyroidism
Data obtained from more than 600 cases

RANGES OF SYSTOLIC BLOOD PRESSURE	PERCENTAGE OF CASES WITH RESPECTIVE RANGE OF SYSTOLIC PRESSURE WITHIN GROUP EXAMINED	AUTHORS
Under 140 mm	64	Kisch ¹⁷⁶
Over 140 mm	36	
Over 190 mm	4	
Under 150 mm	70	Bisgard ²⁷⁷
Over 150 mm	30	
Over 200 mm	3.4	
Under 140 mm	56.6	Labbé ¹⁸²
140-170 mm	25.7	
170-200 mm	14.0	
Over 200 mm	3.7	
Under 140 mm	42	Addarii ²¹
140-170 mm	43	
170-200 mm	10	
Over 200 mm	5	
Hypertensive	27	Brauch ²⁷²
Hypertensive	12	Bach & Bourne ¹⁰¹
Hypertensive	25	Tillgren & Sundgren ²¹¹⁸

rule; (b) that major degrees of systolic hypertension are not common in hyperthyroid patients, (c) that the most characteristic peculiarity of the thyrotoxic blood pressure pattern is an increase not of the systolic blood pressure level but of the pulse pressure.

The latter phenomenon, often referred to as "Pende's sign", exists both in systolically hypertensive and normotensive cases. In the latter, it is manifested by an absolutely low diastolic pressure. It is, in general, more marked in males than in females²²⁷⁵. Its underlying mechanism seems to be

a dilatation of peripheral vessels which appears analogous to that elicited by epinephrine^{1190, 1207}. The causal connection of the elevated systolic pressure in a certain number of hypertensive thyrotoxic cases, and of the augmented pulse pressure, with the exaggerated thyroid function, is evidenced not only by their statistically demonstrable coincidence but also by their joint disappearance following thyroidectomy^{121, 122}.

The existence of a certain quantitative relationship between basal metabolism, pulse pressure and heart rate has been used for an approximate estimation of the basal metabolic level by application of Read's formula: $0.73 (\text{heart rate per minute} + 0.74 \times \text{the pulse rate}) - 72 = \text{BMR}$. However, the results obtained with this formula are not accurate enough to replace the actual determination of the oxygen consumption^{123, 127}. The

TABLE 2
Pulse Pressure in Hyperthyroidism

RANGE OF PULSE PRESSURE	PERCENTAGE OF CASES WITH RESPECTIVE RANGE OF PULSE PRESSURE IN EACH GROUP EXAMINED BY:	
	Lehmann ¹²⁰⁸	Adair ¹²¹
30-40 mm	10	3
40-50 mm	14	11
50-60 mm	16	19
60-70 mm	19	20
70-80 mm	14	15
80-90 mm	9	11
90-100 mm	8	9
Over 100 mm	10	12

liability of the systolic pressure level in thyrotoxic individuals¹²² and sex differences¹²²⁰ add to the unreliability of such calculations. The magnitude of the pulse pressure can be increased by physical exercise¹⁰⁷³ and particularly by the subcutaneous injection of 0.5 mg of epinephrine which may easily depress the auscultatory diastolic pressure tone to zero¹²²¹. This reaction appeared so regularly in some cases that it was used for the evaluation of the therapeutic efficacy of iodine treatment which made it disappear¹²²⁴.

Physical examination of thyrotoxic patients reveals frequently the presence of conspicuously vigorous pulsations of the carotid arteries and the epigastrium, reminiscent of the Corrigan pulse of aortic insufficiency.

Comparing the blood pressure situation as it presents itself in thyrotoxicosis with the pressor effects of epinephrine (p. 145), one is struck by the remarkable parallelism which concerns likewise the concomitant cardiac dynamics. More will be said about this in the section on the heuristic

significance of hyperthyroidism. It may only be mentioned here that the type of hypertension seen in thyrotoxicosis differs from essential hypertension in the same respects as the type of hypertension induced by infusion of epinephrine: the diastolic pressure is normal or low, the systolic pressure is only moderately elevated, and heart action is rapid. It is interesting to note that in a group of thyrotoxic cases with marked systolic hypertension from 180 mm Hg upward, the diastolic pressure level was also elevated, e.g., 250/120, 200/100, 182/100, 180/110, 230/140²⁷⁷. In other words, these cases displayed the typical features of essential (nor-epinephrine-like) hypertension rather than those of thyrotoxic (epinephrine-like) hypertension. In about one-half of a series of hypertensive thyrotoxic patients, thyroidectomy was not followed by a reduction of the systolic and diastolic pressures, some of them progressed even to higher levels²⁷⁷. This seems to indicate that these latter patients suffered from genuine essential hypertension, coexisting with the thyrotoxic state, but causally independent of it. The fact that some of the hypertensive thyrotoxic patients, whose pressure had become more or less normalized following thyroidectomy, still responded to the cold pressor test and to exercise with exaggerated elevations of the blood pressure, seems to justify the assumption²⁷⁷ that "the relation of hyperthyroidism to hypertension in these cases is provocative" and that "hyperthyroidism merely precipitates or exaggerates hypertension which is latent".

Hemodynamics

The *cardiac output* or minute volume (i.e., single stroke volume multiplied with the number of heart beats per minute) is regularly increased in thyrotoxicosis^{678 1047 2041}. Muscular exercise provokes an additional excessive rise of the cardiac output²²⁷⁵. This augmentation of blood flow in hyperthyroid individuals is largely accounted for by the accelerated heart rate, but the individual stroke volume was also found more or less increased, as a rule, by the majority of investigators^{46 129 764 1047 1661 1937 1965 2021 2716} with only a few dissenting opinions^{2041 2725}. The cardioballistogram of thyrotoxic patients reveals abnormally large impacts^{2259 3220} which revert to normal after successful treatment²²⁵⁹. Distortions of the form of the cardioballistogram are suggestive of accompanying heart disease³²²⁰.

The *total circulatory volume* is either unaltered or only slightly increased in thyrotoxicosis^{502 764 1129 2356}, but the velocity of blood flow has been shown to exceed normal limits by far^{130 302 764 2126 3253}. The pulse wave velocity was likewise found to be greater than normal¹¹. Peripheral blood flow^{8, 3252}, especially in the musculature³⁴⁵ and skin²⁹¹⁸ tends to be distinctly increased. The latter is plainly recognizable by the flushed appearance and warm surface temperature in most of these patients. The behavior of

the skin vessels is perhaps the only cardiovascular feature of thyrotoxicosis which seems to differ from the effects produced by epinephrine on the cardiovascular system of most normal individuals. However, it has been shown that in the same vessels which are constricted by larger doses of epinephrine, small amounts can exert a dilating action²⁶⁷. Furthermore, intravenously injected epinephrine elicits in menopausal women flushing of the skin^{268, 269} instead of the surface vasoconstriction of normal individuals. This seems to indicate a specific alteration of skin vessel reactivity which menopausal women, thyrotoxic patients and a minority of otherwise normal individuals have in common. The intimate functional relations between the sympathomimetic amines and histamine²⁶² and the fact that certain autonomic nerve fibers release histamine²⁶¹ are probably involved in these reactions. Dermographism is a common phenomenon in thyrotoxic individuals²⁶⁷.

Some capillary microscopic observations suggest that the caliber of the individual visible skin capillary is reduced in thyrotoxic patients while the small cutaneous arterioles are dilated²³⁰ and the velocity of the blood flow through the capillaries is markedly accelerated²³⁰.

There are some differences of opinion regarding *venous pressure* in hyperthyroidism. Some workers found it to be normal, as a rule²⁰², while others^{264, 267} reported elevations. These discrepancies are probably to be explained by the different numbers of cases with beginning or developed cardiac failure which were included in the respective series of patients examined²³¹.

Heart Rate; Palpitations

Tachycardia is one of the most constant classical signs of thyrotoxicosis but, as has been emphasized before, regarding all details of the thyrotoxic syndrome, one may encounter exceptions even in this respect, in that the heart rate may appear persistently or temporarily within normal limits (lit., see³²⁰). In at least 75 per cent of all cases²³⁰, cardiac action is permanently accelerated to rates somewhere between 90-160 beats per minute, even at complete physical rest and during sleep^{212, 262}. Physical exertion and emotional excitement tend to elicit marked further accelerations^{11, 1060}. In some patients, excessive tachycardias of the paroxysmal type have been observed, particularly during the early morning hours^{11, 260, 1094}.

The fact that in a case of heart block the auricular rate was increased through thyroid hormone action while the ventricular rate was not affected²⁶ suggests that the thyrotoxic tachycardia is provoked, at least in part, by means of the sinus mechanism.

Experimental evidence²⁵² makes it probable that cardiac acceleration in hyperthyroidism results not only from an alteration of the sensitivity of

the heart to physiological cholinergic and adrenergic stimuli but also from an actually increased intracardial liberation of epinephrine. These and other related observations (p. 35 ff.) are likely to offer a satisfactory explanation of the apparently exaggerated intrinsic epinephrine action on the heart in the absence of a demonstrable increase of circulating epinephrine²⁶⁷¹ and of other criteria which would prove an increased epinephrine output from the adrenals²⁹³¹. Where tachycardia is missing, one might suspect a secondary vagal interference, perhaps mediated by the Bezold-Jarisch reflex mechanism, rather than a primary low adrenergic tonus.

The subjective sensation of palpitations, while quite annoying to many patients with thyrotoxicosis, is hardly felt by others. It probably depends on central nervous sensory responsiveness and not on heart action and metabolism *per se*.

Pericardial friction has been noticed in connection with thyrotoxicosis in from 10-50 per cent of the cases by some authors³³⁰⁴. The writer observed it in one case of thyroid over-dosage.

Cardiac Arrhythmias

No other form of cardiac arrhythmia is such a common event in thyrotoxic individuals as auricular fibrillation. While it tends to occur in short, transient bouts during the early stages of the disease, it often establishes itself finally as a permanent condition, unless this is prevented by adequate therapy. Patients in whom auricular fibrillation persists are placed somewhat arbitrarily by some clinicians¹²⁹⁰ into the category of "thyrocardiacs" in contrast to those afflicted only with paroxysmal attacks. The incidence of auricular fibrillation in thyrotoxic patients has been described as being about 40 per cent^{1607 2275} concerning the paroxysmal type, and 5.2 per cent²²⁷⁵ to 5.8 per cent¹⁶⁰⁹ concerning the permanent type. No relationship could be established between the occurrence of auricular fibrillation on one hand and severity of thyrotoxic symptoms or height of basal metabolic rate on the other^{390 1290 3145}. Prolonged duration of the hyperthyroid state^{1290 1595 3610}, advanced age^{890 1290 1347 2207} and the male sex^{1290 2207} seem to favor the development of auricular fibrillation in general. Its progression into a persistent disturbance of heart rhythm has been considered as being enhanced by the pre-existence or co-existence of other more or less independent forms of heart disease (hypertensive, coronary, rheumatic, syphilitic^{1060 2035}). The presence of severe cardiac failure of purely thyrotoxic origin seems likewise to contribute to the onset of permanent auricular fibrillation^{1347, 1607, 3029}.

The mechanism and origin of auricular fibrillation in thyrotoxicosis is as problematic as in other forms of heart disease. However, the observation that acetylcholine can cause the auricles to fibrillate²⁹⁹⁹ and that acetyl-beta-

methyleholin-chloride (meecholy) can convert the normal cardiac rhythm of hyperthyroid patients into auricular fibrillation²⁴² seems to support the contention that the latter may be also spontaneously produced by the interaction of cholinergic and adrenergic factors on the auricular myocardium. Indirect evidence for increased vagal activity as a probable contributing cause of auricular fibrillation in the thyrotoxic heart has been derived from the presence of prolonged P-R intervals in thyrotoxic individuals²¹. Vagal reflexes can be elicited from the auricles themselves if their walls are exposed to increased pressure from the inside (Bezold-Jarisch reflex)^{49 164 165}.

Certain instances of auricular fibrillation in patients with questionable hyperthyroidism but with a persistently or temporarily elevated basal metabolism have been ascribed to a hypothalamic-sympathetic-adrenal mechanism²¹⁰.

Although auricular fibrillation is not as common an occurrence in normal animals and humans after injection of epinephrine as its appearance in hyperthyroid individuals, it has been produced through injection of epinephrine in a number of instances^{167a 215 216 217a, 218a 219 220}, one of them having been the writer himself²⁴⁶, and it is sometimes seen during paroxysms in pheochromocytoma cases^{80 90 100, 136}. Thus, a potentiation of epinephrine action which we have postulated for other cardiovascular features of thyrotoxicosis can be accepted as a possibility also regarding the phenomenon of auricular fibrillation.

Other cardiac arrhythmias, such as auricular flutter^{16, 172 174 227 227}²⁴⁶, paroxysmal tachycardias of different types^{90, 223 191, 201} and sino-auricular block^{227 228 240} have been reported only in rare instances of thyrotoxic patients and their direct causal connection with the overactive

thyroid gland, although somewhat more common^{120 140}, are equally unspecific. Ventricular fibrillation seems to have been observed in only one single case of hyperthyroidism²³ and ventricular pre-fibrillation in another²⁹¹. In two cases of sudden death, the involvement of ventricular fibrillation was assumed by inference, without electrocardiographic proof²⁷.

Some isolated observations of relative or absolute bradycardia^{47, 247, 258} are difficult to explain. The effectiveness of vagal stimulation is generally diminished in the thyrotoxic heart (p. 37), but this seems to be a rather than an absolute fact. The effect of digitalis is also diminished in the hyperthyroid heart, even more so in the hyperthyroid heart with a rapid rate.

was interpreted as indicating an increased absolute sensitivity of the thyrotoxic heart to both acetylcholine and "sympathin"²⁶⁵⁸. A delicate balance is apparently being maintained between the two alternatives, which usually tends toward the adrenergic side, but which may also tip over into the opposite cholinergic extreme under certain still undefined circumstances. It is worthy of note that the thyroid hormone seems to inhibit the enzymatic inactivation of both epinephrine, nor-epinephrine and acetylcholine²¹⁵⁷.

Congestive Heart Failure

Before the modern development and general early application of efficient therapeutic methods for thyrotoxicosis had taken place, the most serious cardiac complication of this disease, congestive heart failure, used to be seen much more frequently than today. Pre-existing manifest or latent "organic" cardiac lesions on one hand, and whatever additional damage the thyrotoxic state may impose upon the heart on the other, are likely to cumulate to such an extent that it is often difficult or impossible in the individual case to gauge the degree of pathogenic effectiveness, contributed by the over-active thyroid as such. Some clinicians^{813 1594 2022} go so far as to deny the possibility of cardiac failure being produced by thyrotoxicosis *per se* in the absence of other forms of cardiac pathology, such as "hypertensive" heart disease, coronary sclerosis, rheumatic valvular lesions, etc. It is undoubtedly true that the break-down of cardiac dynamic efficiency is accelerated in such cases by the metabolic maltreatment which an excess of thyroid hormone inflicts upon an already handicapped myocardium. The relatively early development of cardiac failure in thyrotoxic patients with *primarily abnormal hearts* ("cardiacs") illustrates this point²⁰³³, which has been described as a "catalytic" effect of thyrotoxicosis upon organically diseased hearts. Nevertheless, there remains a substantial number of thyrotoxic cases with congestive failure (râles, dyspnea, cough, hydrothorax, enlarged liver, peripheral edema) in which no indication of pre-existing heart disease could be found. Likoff and Levine²⁰³³ diagnosed congestive failure in 50 per cent of 78 primarily "cardiac" hyperthyroid patients and in 6.3 per cent of 331 "non-cardiac" cases. Similar results (52 and 13 per cent respectively) were obtained by other authors¹²⁹⁰. It thus appears that the pre-existence of "organic" heart pathology, although greatly enhancing the development of congestive failure in thyrotoxic individuals, is no indispensable prerequisite for it, in other words that hyperthyroidism alone can also produce congestive failure.

Data concerning the frequency of occurrence of auricular fibrillation in thyrotoxic patients with congestive failure vary between 65 per cent¹²⁹⁰ and 90 per cent¹⁶⁰⁷.

The total incidence of congestive failure (with and without accompanying "organic" heart lesion) was calculated as 3.9 per cent²²³, 5.2 per cent¹⁰⁴, 15 per cent²⁰³ and 18.5 per cent²⁰ respectively in four different large groups of thyrotoxic patients. It has been justly emphasized^{202, 203} that the presence of edema alone is not sufficient in thyrotoxic patients to classify them as having heart failure.

The type of morphological thyroid pathology (parenchymatous vs. adenomatous) is of doubtful significance for the development of heart failure²⁰. No definite relationship seems to exist between the general severity of thyrotoxicosis and its tendency to give rise to cardiac complications. However, a long duration of unchecked hyperthyroidism, advanced age, and the female sex seem to favor the establishment of congestive cardiac failure²⁰.
^{1290 2034} It has also been observed as a complication of "thyrotoxicosis factitia"²⁰³⁴.

Diagnostically difficult situations arise in thyrotoxic patients with congestive failure who do not display the tell-tale signs of distinct thyroid enlargement, exophthalmos and tremor, and in whom the cardiac phenomena, elevated basal metabolism, nervousness, etc., may be ascribed to "primary" or "organic" heart disease just as well, especially also when a pre-systolic murmur, a snapping first sound, a marked left auricular dilatation and auricular fibrillation evoke the impression of rheumatic mitral stenosis^{225 227 2034}. For this entire, not too well defined group, the term "masked thyroid cardiacs" has been coined^{20 203 243}. Since antithyroid treatment, surgical or medical, offers a relatively bright prospect in such cases, its advisability has been strongly emphasized²⁰³. The writer doubts, however, that therapeutic success, obtained by thyroid inactivation, is sufficient *ex post* evidence for a primarily exaggerated function of the thyroid gland in any given case of heart failure, because this type of therapy has proven effective also in euthyroid cardiac patients (p. 508). The elimination even of normal quantities of thyroid hormone can exert beneficial effects by desensitizing the myocardium to the injurious chemical influence of the adrenergic sympathomimetic catecholamines.

Attention has been called by several authors^{150 2035 2276, 2632, 2511} to the striking similarities between thyrotoxic heart disease and heart failure.

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Furthermore, an excessive accumulation of epinephrine and related catecholamines was shown in the heart muscle of thiamin-deficient rats^{2064, 2720}. Thus, there seem to exist definite pathogenic relations between vitamin B₁, the thyroid, the adrenergic neurohormones, and congestive failure in thyrotoxicosis.

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effects may arise in the myocardium from either an excessive influx of adrenergic neurohormones in the presence of normal cardiac sensitivity, or from a normal influx of adrenergic neurohormones into a heart muscle which is over-sensitized by an excess of thyroid hormone, or from a combination of both factors. The problem of the ultimately adreno-sympathogenic biochemical nature of the anginal syndrome will be discussed in detail on p. 373 ff. It should be mentioned here, however, that an essential element in the origin of anginal pain seems to be the suddenness of hypoxiating adrenergic neurohormonal extra discharges, which reach the myocardium. In thyrotoxicosis, there is no reason to assume any unusually intense, acute bouts of adrenergic neurosecretory activity. Over-sensitization of the heart to epinephrine through excess thyroid hormone is a permanent condition, and it seems probable that the rather static character of this situation, together with a simultaneously increased sensitivity to vagal (cholinergic) stimuli¹⁸⁰⁹, may account for the comparative rarity of angina pectoris in hyperthyroidism.

Electrocardiographic Changes

The amount of literature devoted to the electrocardiographic changes occurring in thyrotoxicosis stands in reverse proportion to the amount of meaningful information deductible from it. The apparent inconsistencies in the results which render their interpretation so difficult seem to arise from the variety of more or less concealed interfering factors which are likely to influence the electrocardiogram in different, even in opposite directions. Such factors are: (a) the presence of complicating "organic" heart disease, (b) the imperceptible progression of the basic functional hormonal action upon the heart muscle into established myocardial damage, (c) the conflicting electrocardiographic effects of "amphotropic" sympathetic and vagal stimulation, the latter of which is usually over-shadowed by the former, but none the less active, according to certain experimental¹⁸⁰³ and clinical¹⁸¹⁴ observations.

If we exclude the cases in which the electrocardiogram is altered by definite coronary sclerosis and other recognizable forms of "organic" heart disease, there remain the following, relatively common electrocardiographic changes which can be attributed with some justification to the thyrotoxic state as such:

- (1) An elevation of the P-wave, mainly in lead II, was described in 26 per cent to 98 per cent of the cases by many observers.^{1445 1703 1803 1831 1874 1886 1887 1811 1812 1813 1815 1816} While some of them consider this phenomenon as within normal proportions to the existing tachycardia^{1803 1815 1816}, there are others^{1804 1817} who ascribe to it pathological significance. With reference to older experimental findings¹⁸⁰⁸ concerning an augmentation of the P-wave

Angina Pectoris

Clinical data concerning the frequency of subjective anginal or anginal-like symptoms in thyrotoxic patients are somewhat contradictory. Special emphasis was placed on the coincidence of these two conditions by Lev and Hamburger¹⁹⁷⁹ in a communication which started the ever-expanding literature concerning the treatment of angina pectoris by inactivation of the thyroid gland. Other observers¹⁷⁹⁰ state that among their material of "thyrocardiacs" there were 11 per cent who complained of angina, whereas among the controls there were only 3.5 per cent. Most reports concerning the coexistence of angina pectoris and hyperthyroidism, while recognizing it as a fact^{11 722 2307, 3207, 3435}, are not very emphatic about it. Indeed, some authors^{3207 3593} declare it as rare. This would seem paradoxical in view of the potentiating influence which the thyroid hormone exerts upon the hypoxia-producing metabolic effect of the sympathomimetic catecholamines on the heart muscle, as it constitutes one of the two most important factors in the origin of anginal symptoms (p. 373 and p. 387). However, an excess of thyroid hormone counteracts at the same time the development of atheromatosis and thus largely prevents the other basic factor which contributes to the pathogenesis of angina pectoris, namely coronary sclerosis (p. 38, 39).

Anginal symptoms almost never make their appearance in thyrotoxic patients below the age of 45¹⁹⁷⁹ or 40 years³⁴³⁵. The male sex³²⁰⁷ is generally more heavily afflicted by genuine angina pectoris than the female sex (p. 420). The actual presence of coronary sclerosis is not always clearly demonstrable (see above) and some authors state explicitly that they are inclined to attribute the pain syndrome rather to a relative coronary insufficiency in proportion to the thyroid-induced extra work performed by the heart than to an absolute diminution of the coronary caliber^{11 607 3201}. In one case of angina pectoris in a thyrotoxic patient, complete absence of coronary sclerosis was found at autopsy³⁶⁴. Although this single observation does not permit any far-reaching generalization, it appears nevertheless interesting and consistent with the above outlined views.

The most convincing proof of at least a partial causal relationship between thyroid function and anginal complaints rests on the frequently striking curative effect of thyroid depression or inactivation, either by iodine treatment¹⁹⁷⁹ or thiouracil^{3200 3435} or thyroidectomy^{1332 1979 3201}, not only in thyrotoxic but also in euthyroid patients with angina pectoris (p. 399 ff).

The borderlines between definitely non-thyrotoxic forms of angina and those in which thyroid over-activity seems to play a more prominent role, are fleeting, in accordance with the fact that identical anoxiating metabolic

this phenomenon were attempted by its earlier observers; but in the light of present-day knowledge regarding the adrenocortical implications of the stress, involved in the procedure of surgical thyroidectomy, it seems conceivable that one might have to deal here with the effect of adrenal cortical and electrolyte alterations.

Certain occasionally reported types of conduction disturbances, changes of the Q-T interval, Wolff-Parkinson-White syndrome, etc., are of minor importance. They are described in special reviews on these subjects^{11 140.}
1207 1214 The arrhythmias of thyrotoxicosis have been discussed on p. 132

In conclusion, it can be stated that out of the bewildering mass of electrocardiographic observations in thyrotoxicosis there emerge a few reasonably circumscribed details which, although of minimal diagnostic usefulness, may be rationally correlated with the concept of an adrenergic neurohormonal mediation between exaggerated thyroid activity and cardiac response: high P and high T (increased sympathetic tone), flat or inverted T, depressed S-T (myocardial hypoxia due to a major degree of chemical interference of intrinsic adrenergic catecholamines in myocardial metabolism), transient post-thyroidectomy T depression (stress-induced adrenocortical effects upon the pre-damaged myocardium).

Roentgenographic Changes of the Heart

As in all other respects which concern the heart of hyperthyroid patients, there are considerable divergencies of opinion regarding its roentgenological characteristics. Here again the not infrequent coincidence with non-thyrototoxic "organic" cardiac abnormalities tends to confuse the issue. However, apart from the controversy in regard to certain details which will be mentioned later, there is at least one feature which can be described as a fairly specific and frequently, though not invariably (30-50 per cent²⁷⁰²), occurring peculiarity of the thyrotoxic heart, namely an unusual prominence of the *conus of the pulmonary artery*^{212 1223 2211 2302 2327 2343 2352. 2350 2348.} Earlier explanations of this phenomenon which tried to interpret it as being caused by mechanical pressure of the enlarged thyroid upon the trachea, or as a constitutional trait^{232 1222}, have been largely abandoned in favor of the theory²³⁰² that an assumed disproportion between dilatation of the systemic vascular bed and lack of an analogous dilatation of the pulmonary circuit would put the latter under increased pressure with resulting dilatation of the pulmonary artery. This view would also seem compatible with the elevation of P2 of the thyrotoxic electrocardiogram (p. 137), in a similar way as a high P2 exists in cases of pulmonary sclerosis. It would likewise agree with the frequently visible expansile pulsations of the pulmonary hilus^{249 2502} within bright, non-congested lung fields²⁴⁶⁶. Certainly, the fact

during sympathetic stimulation, the prevalent sympathetic tone of hyperthyroidism was held responsible for it; but an increased auricular filling due to hemodynamic factors (increased resistance in the pulmonary circulation) was also thought to be involved^{1203, 1884}. No clear relationship between height of the P-wave and severity of the clinical syndrome could be established from case to case^{345, 1035, 1669}. However there seems to exist a certain connection between the behavior of the P-wave and the clinical course in individual patients, which includes normalization after thyroidectomy²⁵⁰⁷.

(2) A high voltage of the QRS complex was stressed as a frequent, even though not regular occurrence by several investigators^{1666, 2095, 2559, 3012, 3159, 3205}. Diminished cutaneous resistance and reduced panniculus adiposus were quoted as contributing factors. It is difficult to evaluate a deviation of the QRS voltage from its individually normal magnitude in any given case of hyperthyroidism without knowledge of its original size, but some significance can be attached to a reduction of QRS voltage after thyroidectomy³²⁰⁷.

(3) Abnormally high T-waves have been recorded in large numbers of thyrotoxic patients^{1025, 1246, 1339, 1619, 1854, 2150, 3207}. They were usually interpreted as an expression of exaggerated sympathetic tone^{1853, 2313, 3207}. Analogous changes of the T-wave were elicited in normal persons by feeding a thyroid preparation¹⁶¹⁹. Thyroidectomy, on the other hand, was seen to reduce the height of the elevated T-waves¹⁹³⁴. It is not possible at the present time to reach any definite conclusion regarding the mechanism underlying the elevation of T. In normals it can be elicited by simultaneous sympathetic and vagal stimulation, e.g. during infusion of nor-epinephrine²⁷⁰⁴ which is accompanied by reflectory vagal action.

(4) The pathologically most important abnormality of the thyrotoxic electrocardiogram is a flattening or inversion of the T-wave with or without depression of the S-T segment in the first and/or second lead. Its apparent inconsistency with previously mentioned findings proves to be only a superficial one, if its presumed dependence on the development of actual myocardial hypoxia is taken into account. In fact, ever since T-wave depressions in thyrotoxicosis had been first described by White and Aub in 1918³⁵⁹⁷, the opinion was generally expressed that flat or inverted T-waves and S-T depressions appear mainly in patients with superimposed myocardial damage^{1737, 1953, 2371, 3207, 3640}. In a number of instances, they were encountered in association with anginal symptoms¹³²². Correlations with the basal metabolic level could not be established^{1669, 3597}. Unless cardiac damage is too far advanced, thyroidectomy is eventually followed by a normalization of previously "anoxic" negative T-waves^{1241, 3159}.

A puzzling finding is the frequent appearance of a temporary flattening or inversion of the T-waves after thyroidectomy^{1223, 1244, 1699, 1934} which may persist for days or weeks. Various rather unsatisfactory explanations for

other cardiac phenomena, such as auricular fibrillation or cardiac failure¹⁰⁶, which were quite arbitrarily represented as independent "complications" rather than as pathogenically intimately related features of thyrotoxic heart disease. As cardiac hypertrophy is one of the typical effects of chronic adrenergic over-action (p. 18), and since adrenergic effects upon the heart are potentiated by the thyroid hormone (p. 35, 36), there seems hardly any reason for continuing the debate as to whether or not thyrotoxicosis has anything to do with the common occurrence of cardiac hypertrophy in thyrotoxic patients. A more interesting and important question is that concerning thyroid-adrenergic-pituitary-adrenocortical interaction in hyperthyroidism and its chemical effects upon the heart. The findings of Beznák and Hajdu¹⁰⁸ that the thyroid hormone sensitizes the heart muscle to the hypertrophy-producing effect of the pituitary growth hormone and that the latter is indispensable for the development of cardiac hypertrophy seems highly significant and a promising clue for further research.

The literature on the subject of microscopic alterations in the hearts of thyrotoxic individuals is dominated by argumentations regarding the thyrotoxic or non-thyrotoxic origin of degenerative, interstitial "myocarditic" and necrotic foci which are more or less frequently seen in the myocardium of hyperthyroid individuals^{109 110 111 120 121 122 123 124 125} with a sizable group of authors^{126 127 128 129 130 131 132 133 134 135} on the oppositional side. The statement made by some^{136 137 138} that thyrotoxicosis does not by itself "produce" cardiac pathology but favors and accelerates the development of cardiac lesions from other causes, may be regarded as a compromise, but it betrays at least a vague recognition of the fact that various types of heart disease are intimately related to each other on the common grounds of a hormonal biochemical mechanism of origin.

Treatment

The treatment of the cardiac symptoms of thyrotoxicosis is essentially identical with the treatment of thyrotoxicosis itself. Purely symptomatic cardiac therapy is ultimately doomed to failure, not only because it does not control the underlying hormonal derangement, but also because the thyrotoxic heart is, in general, less responsive to the treatment.

that the enlargement of the pulmonary conus often disappears after thyroidectomy^{2221, 2302}, serves as strong evidence against its congenital nature.

Quite frequently the prominent pulmonary conus is mistaken for a dilated left auricle and thus may lead to the erroneous diagnosis of rheumatic mitral stenosis, especially in the presence of a pre-systolic murmur. With careful examination of the heart in oblique and lateral projection, such errors can be avoided^{2221, 2330}.

Enlargements of the auricles as well as of the ventricles do occur, however, if other forms of heart disease are present simultaneously, or if cardiac failure of thyrogenic origin supervenes.

Roentgenographic data concerning the size of the ventricles in thyrotoxicosis are somewhat contradictory. Some authors^{2227, 2249, 2330} claim to have seen general enlargements of the heart in 45-83 per cent of their cases. A "ham" shape of the cardiac silhouette with dilatation of the left ventricle and auricle²³³⁰ or a globular outline¹⁰⁶⁰ with bilateral enlargement have been described as characteristic, particularly in elderly patients²³⁴⁹. Although a substantial part of such alterations is probably to be attributed to co-existent "hypertensive", coronary or rheumatic heart disease¹⁰⁶⁰, there still remain those rather numerous cases in which thyroidectomy or other forms of anti-thyroid treatment are followed by a reduction of the heart shadow to about normal dimensions^{749, 2323, 2327, 2328} as an indication of the at least partial thyrogenic origin of its former enlargement.

In some instances, the heart of thyrotoxic patients was even found to be smaller than normal and to decrease further in size in the erect position, not unlike the heart in Addison's disease²⁷⁰².

Morphological Cardiovascular Changes

Very little is to be found in the literature concerning the presence or absence of arteriosclerotic lesions of the vascular tree in connection with thyrotoxicosis. The lack of statistical exploitation of this point, together with the experimentally demonstrable protective action of the thyroid hormone against intimal lipid depositions (p. 38), seems to suggest that there is no statistically tangible tendency toward arteriosclerosis in thyrotoxic patients. This negative statement applies also to the kidneys in which "nothing of note beyond slight vascular changes and occasional hyalinized glomeruli" was detected²²⁷⁵.

As far as morphological changes of the heart are concerned, it is widely agreed that *hypertrophy of the heart* constitutes a very common feature

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more recently been amplified, if not superseded, by the antithyroid drugs of the thiourea group which block the enzymatic incorporation of iodine into the thyroid hormone^{57, 72, 573}. Iodine alone, administered during 10-14 days, is still useful in milder cases which are considered good surgical risks^{212, 245}, but for patients beyond the 45th year and with serious cardiac complications, the use of propyl-thiouracil^{100, 212} or radio-iodine²⁴⁵ is preferred. The faster action of iodine is compensated for by the more completely normalizing antithyroid effect of the thiourea compounds as well as of radio-iodine. If propyl-thiouracil is combined with iodine, the latter should be given during the last three weeks or so of the pre-operative propyl-thiouracil treatment period and not in the beginning, as this would delay the action of the antithyroid drug¹⁰⁰. The new compound iodothiouracil is said to obviate such difficulties²¹².

Cardiac symptoms which persist after subtotal thyroidectomy are likely to be caused by non-thyroid factors and must be treated accordingly.

The usefulness of *thiourea compounds* for prolonged conservative treatment of thyrotoxicosis is still under debate despite the spectacular initial successes achieved by Astwood⁸⁶ and others^{153, 201, 2120, 2120, 2124, 2127} with thiouracil, propyl- and methyl-thiouracil. There are the following points which make it unlikely that these drugs will become the generally accepted therapeutic choice for the long-range treatment of hyperthyroidism: (a) their potential toxicity (granulopenia, fever, rash, gastric symptoms, arthralgia, in 2 per cent of the cases treated with propyl-thiouracil and in 7 per cent of those treated with methyl-thiouracil¹⁰⁰), which requires constant medical supervision, (b) the relatively frequent occurrence of relapses (35 per cent^{227, 256} to 51 per cent of the cases¹⁶⁴, which have been observed at time intervals from one week to 14 months after discontinuation of the drugs²¹²⁴, as compared with only about 10 per cent recurrences after subtotal thyroidectomy¹²⁰⁰; (c) the persistence or even further enlargement of the goiter¹⁵⁹, (d) the necessity for prolonged continuous medication (6-18 months)^{159, 274} with uncertain prospect of lasting results; (e) the inferior efficiency in suppressing auricular fibrillation^{152, 220}.

The dosage for propyl- and methyl-thiouracil is 200-500 mg daily, according to the size of the goiter^{159, 2120}.

Almost no detailed information is available from the literature regarding the specific response of blood pressure, heart rate, heart size, electrocardiogram, etc., to the treatment with thiourea compounds, in contrast to the abundant flood of statistical data from untreated patients. While some observers¹²⁹⁰ profess to have seen only little improvement from thiouracil in thyrocardiac cases, the reaction of a small, unidentified number of patients with congestive failure within another group of thyrotoxic cases

tinues^{1060, 3593}. Consequently, these medications, as well as aminophylline, diuretics, salt restriction and rest, while useful in carrying the patient with congestive heart failure through the preparatory period before surgery or before one of the conservative antithyroid treatments has taken full effect, cannot be considered as sufficient by themselves to normalize the patient's cardiac status.

In contrast to certain older forms of treatment (ice packs on the neck, ergotamine, x-ray irradiation of the thyroid, etc.), there are three types of antithyroid therapy which yield excellent results. Their comparative merits and shortcomings have not yet been evaluated with absolute finality.

Surgery is definitely indicated in all cases with proven or suspected malignancy. Some workers extend the absolute indication for subtotal thyroidectomy to all thyrotoxic cases with nodular goiters^{159, 2555}. It is obviously also the method of choice if mechanical compression of adjacent structures (trachea, esophagus) by the enlarged gland creates a problem, or if the patient wants to get rid of an unsightly goiter for cosmetic reasons.

While the association of thyrotoxicosis with severe heart lesions, especially in elderly patients, is regarded in some quarters^{662 1237 2555} as an argument against surgical interference, there are those who advocate it on the contrary because of its very usefulness in repairing cardiac damage and because of its offering the best possible guarantee against later recurrences^{1060 1290 1996 2033}. The operative mortality of "thyrocardiacs" varies according to different statistics between 0 per cent²⁰⁹⁹ and 4.25 per cent¹⁵⁹⁶, that of non-cardiacs between 0.08 per cent¹⁵⁹, 0.2 per cent⁴¹⁹, and 2.6 per cent²⁰³³. Lahey and Hurvthal¹³⁹⁶ reported restoration of cardiac compensation in 95 per cent of their large series of cases, and abolition of auricular fibrillation in 71.5 per cent. Only 1.5 per cent of the cardiac patients remained completely incapacitated on account of heart failure. The value of the electrocardiogram as a criterion of the surgical risk of thyroidectomy is questionable¹²⁷⁰.

Not infrequently (in about 16 per cent⁴⁹⁴), auricular fibrillation appears after thyroidectomy and may persist for a few days¹¹⁵², even in patients who had never fibrillated before^{813, 894 1060 1152 2152}. It has been ascribed to the flooding of the body with thyroid hormone from the dissected gland¹²⁴⁷.

Persistent auricular fibrillation tends to disappear within a matter of weeks or months after thyroidectomy in about one-half of the cases^{54, 890, 1290}. Medication with quinidine in the immediate post-operative period improved the results substantially⁵⁴.

As far as the specific preparation for surgery is concerned, the use of iodine (Lugol's solution), whose mode of action is still unexplained⁵⁷, has

add the category of "thyrocardiacs" as a third example of conspicuous hormonal-chemical interference in cardiovascular function and structure with pathogenic implications concerning also the common forms of angina pectoris and congestive heart failure (pp. 387 and 491). The initiative of the clinicians of the Boston school who introduced the methods of thyroid

TABLE 3

Comparison of Neurovegetative and Cardiac Phenomena Characteristic for the Thyrotoxic Syndrome and for the Action of Epinephrine, Administered to Normal Humans or Animals

	THYROTOXICOSIS	INDUCED EPINEPHRINE ACTION
Oxygen consumption	Wastefully increased	Wastefully increased (especially proven for heart)
Heart rate	Increased	Increased
Minute volume	Increased	Increased
Peripheral vascular bed	Dilated	Dilated
Diastolic pressure	Normal or low	Normal or low
Systolic pressure	Moderately elevated or normal	Elevated
Pulse pressure	Increased or normal	Increased or normal
Heart rhythm	Auricular fibrillation (common)	Auricular fibrillation (occasional)
T wave	(a) Flat, inverted (advanced cases) (b) Sometimes elevated	(a) Flat, inverted (large doses) (b) Sometimes elevated
Myocardium	(a) Hypertrophic (advanced cases) (b) Necrotic foci (advanced cases)	(a) Hypertrophic (prolonged application) (b) Necrotic foci (large doses)
Blood sugar level	Increased	Increased
Perspiration	Increased	Increased
Skin vessels	Dilated	Dilated in menopausal women but usually constricted in normal subjects

One more point which requires comment is the clinical observation which the increased metabolism of myocardial metabolism is represented as a "wasteful" process. This is a statement of other tissue metabolism. It is not a statement of myocardial metabolism by introducing an element of wishful teleology into a subject which demands

seems to have been favorable¹²³⁷, and in 12 patients with congestive failure who were treated with thiouracil (plus digitalis), compensation was restored, whereas auricular fibrillation persisted in all but one of them⁶⁵².

The newest and perhaps the most promising type of anti-thyroid treatment is the oral administration of *radioactive iodine* (I^{131} , 8 days half-life) which was introduced in 1942 by Hertz and Roberts¹⁴³⁴. Its therapeutic action is due to the destruction of the over-active thyroid tissue. Side effects are negligible, except for a certain degree of tenderness of the shrinking thyroid one to three days following the ingestion of the active material (1.5-14.5, average 5 millicuries²⁶⁴²) which may have to be repeated once or twice at intervals of about eight weeks in partially refractory patients¹⁷⁴¹. Reports on the effectiveness of this therapy^{308, 2274, 2642, 3195, 3563, 3638} indicate excellent results in 60-100 per cent of all cases, developing within one to four months, with only a minimal tendency toward recurrence observed so far. Myxedema appears more readily than after subtotal thyroidectomy^{1331, 3568} and may require substitutive thyroid treatment. Good results were apparently obtained also in some thyrocardiac patients, included in radio-iodine-treated groups of cases^{1331, 2553}. Here again no details are reported.

There is still a number of questions to be answered regarding the safety and long-range efficiency of the treatment with radio-iodine, but the prospect appears encouraging from all available information.

Heuristic Aspects of the Thyrotoxic Cardiovascular Syndrome

Most of the neurovegetative and cardiovascular functional characteristics of the thyroid syndrome bear a striking resemblance to the effects of epinephrine on corresponding organs and functions. In fact, this resemblance, which is represented in Table 3 by an eloquent list of analogies, suggests a real identity.

Sympathomimetic catecholamines are constantly present in varying amounts within all sympathetic innervated tissues, especially of the cardiovascular system, and ready to cause trouble. We do not yet know in which way the potentiation of adrenergic action through the thyroid hormone takes place, whether the underlying changes occur on the cell membranes or within the protoplasm of the cardiovascular cells, whether they involve a protection of the active catecholamines against enzymatic destruction¹¹², or whether they consist of a direct molecular alteration of these catecholamines themselves. Whatever the finer mechanism may be, the fact of epinephrine potentiation through the thyroid hormone appears to constitute the basic principle of the cardiovascular features of thyrotoxicosis.

To the previously discussed "experimental" clues, supplied by Nature, in creating clear-cut "adrenocardiacs" and "corticocardiacs", we can now

Hypothyroidism (Myxedema)

Endocrine Pathology

Since the recognition of a causal connection between the clinical syndrome of myxedema and the thyroid gland by W. N. Ord in 1878, only little has been learned regarding the fundamental causes of thyroid under-function or non-function, except in the case of artificially induced myxedema as a sequel of total thyroidectomy or due to an over-dosage of thiourea compounds, of thiocyanate¹⁷², or of radio-iodine. Thyroiditis may be followed by myxedema in rare instances¹⁷³. In some cases, the functional break-down of the thyroid gland occurs as the result of a primary atrophy or tumor of the anterior lobe of the pituitary and consequent lack of the thyroid stimulating hormone (THS) (p. 175), but here again the ultimate starting mechanism remains shrouded in obscurity. The facts that the female sex is about five to ten times more frequently afflicted than the male^{174, 175}, that the disease shows a predilection for middle-aged women past 40, especially for those who had given birth to many children¹⁷⁶, for persons of the psoric type, and for the inhabitants of the British Isles and the Baltic coast of Germany¹⁷⁷, do not contribute much toward a clearer understanding. Cretinism, which is a complicated disturbance with marked cerebral deficiencies and with hypothyroidism as a side phenomenon, constitutes in itself a problem which falls beyond the scope of the present discussion.

Autopsies of untreated cases have become quite rare in our times, but by comparison with older reports it seems that specific hormone treatment does not affect the morphological characteristics of the underfunctioning thyroid significantly. They consist essentially of atrophy and replacement of the parenchyma by connective tissue which may contain some remnants of fairly normal epithelium.

Morphological changes in the pituitary of myxedematous individuals are not well defined. There may be an enlargement of the pituitary^{178, 179}, an increase of the eosinophil cells^{180, 181}, or, on the other hand, complete atrophy¹⁸². In this latter type of "pituitary myxedema", the adrenals become atrophic. In the ordinary form of myxedema they do not appear remarkable¹⁸³ but functional indications of a reduced cortical activity have been observed in patients with hypothyroidism^{184, 185}.

General Symptomatology; Diagnosis

Due to the slow and insidious development of myxedema, the earlier phases of the disease remain often unrecognized for months or years. The fully established "athyroid" syndrome, however, is very characteristic. In most respects, it appears as the exact opposite of the hyperthyroid syndrome (1) small, non-palpable thyroid gland; (2) dull, expressionless face;

strictly detached, objective thinking in terms of cause and effect and in which the preservation of that state of affairs which we commonly designate as "health" must not be regarded as a goal but merely as a process. It is our task to analyze its biological mechanism and not its metaphysical purpose. The teleological interpretation of the cardiovascular effects elicited by an exaggerated thyroid secretion has been convincingly refuted by the experimental observations of Rasmussen²⁷⁴⁵ and Leblond and Hoff¹⁹⁴⁹.

Cardiac damage in thyrotoxicosis is due to immediate hormonal action upon the heart muscle. It is, in all likelihood, mediated by a potentiation of stimulating and ultimately hypoxiating effects of intrinsic adrenergic catecholamines through the thyroid hormone. A possible secondary participation of adrenal corticoids in the later stages of the thyrotoxic cardiovascular syndrome remains to be elucidated.

Summary

The cardiovascular situation in states of thyroid hyperfunction is characterized by tachycardia, increased cardiac output, increased pulse pressure, a tendency toward auricular fibrillation, cardiac hypertrophy and ultimate congestive failure. In part of the cases, the two last-named features are due to an aggravation of pre-existing cardiac damage ("hypertensive", coronary, rheumatic, syphilitic), but there remains a substantial number of instances in which the heart lesions must be attributed to hormonal interference alone. This is evidenced by the complete restoration to normal of severely pathological hearts after timely abolition of thyroid over-activity. Subtotal thyroidectomy, the safety of which has been improved to a maximum, even in advanced "thyrocardiacs", by the pre-operative use of iodine and antithyroid drugs, is still the method of choice for the majority of cases. It may have to yield to the treatment with radio-iodine, however, if the latter should prove as safe and as lastingly effective as present experiences seem to indicate. Propyl- and methyl-thiourea are losing ground as tools of exclusively conservative therapy because of various disadvantages connected with their application.

Numerous experimental and clinical observations make it probable that the cardiovascular manifestations of hyperthyroidism are essentially caused by a potentiation of the biochemical effects of the ubiquitous adrenergic catecholamines, especially of epinephrine, upon the cardiovascular cells. The analogies of the characteristics of epinephrine action, on one hand, and of the clinical symptomatology of "thyrocardiacs", on the other, are striking. Certain indications suggest a simultaneous, though less conspicuous vagal overactivity.

The relative infrequency of angina pectoris in thyrotoxic individuals is probably due to the antiarteriosclerotic action of the thyroid hormone.

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(3) pale, slightly yellowish, pasty, dry skin; puffy eyelids; lack of perspiration; (4) coarse, brittle hair, becoming sparse, especially on the eyebrows, brittle fingernails; (5) hoarse, husky voice; slow, poorly articulated speech, large, heavy tongue; (6) gain in weight; (7) general weakness and fatigue; (8) over-sensitivity to cool temperature; (9) constipation; (10) decrease of libido; menorrhagia or amenorrhea; (11) mental apathy with impairment of memory and initiative but not necessarily of reasoning ability; drowsiness

In the classical syndrome, the *basal metabolic level* is invariably depressed 25–40 per cent or more. As in hyperthyroidism, the BMR value per se is not absolutely pathognomonic^{350, 374}. Moderately lowered BMR readings, e.g., –20 per cent, may be due to other causes, usually of an unknown nature (possibly a low sympathetic neurosecretory and low adrenocortical activity); but a basal metabolism of –30 per cent or below, if accompanied by other clinical features, suggestive of myxedema, provides strong diagnostic evidence.

Another valuable laboratory criterion is an elevation of the *blood cholesterol* level, particularly if associated with a low basal metabolism. With only few exceptions the readings are found higher than 250 mg per cent^{1601, 2240} and may reach 500 mg per cent or more

The *protein-bound iodine in the serum* tends to be low (below 3 gamma per cent)²⁹¹⁹ and ingested tracer doses of radio-iodine are almost completely excreted with the urine because of the absence of active thyroid tissue which would retain this material in the body²¹¹⁶. The urinary creatine excretion is about normal²¹²⁷. Anemia is often seen as an accompanying symptom. Untreated patients in an advanced stage of myxedema can drift into a state of cachexia and, unless they succumb to cardiovascular complications (see below) or to an intercurrent infection, they may end up in a fatal coma.

Blood Pressure

Nothing very definite can be said about the blood pressure in myxedema. Apart from not too uncommon cases of hypertension whose origin is probably unrelated to the hypothyroid state, there are no characteristic deviations from normal. Low systolic and diastolic pressures with a small pulse pressure are sometimes seen^{1060, 2275} but are not the rule. Treatment with thyroid hormone may reverse the situation and either elevate the blood pressure to abnormal levels²²⁸⁴ or depress an existing hypertensive level toward normal (especially the diastolic pressure)²²⁷⁵. These paradoxical reactions are probably to be explained, at least in part, by the conflicting effects of the thyroid-potentiated epinephrine-action upon the cardiac output on one hand, and upon the vascular bed on the other (p. 6) Total

ablation of the normal thyroid in humans was not found to be followed by any significant alterations of the blood pressure⁴⁴. Means²⁷² quotes the case of a 92-year-old myxedematous woman who had been continually treated with thyroid for 50 years. During the last 20 years of her life she was hypertensive and her blood pressure reached levels as high as 300/160.

The pressor and cardioacceleratory effects of epinephrine were found diminished in originally euthyroid patients after total thyroidectomy^{190, 202}.

Heart Rate and Hemodynamics

The heart rate is usually decreased in myxedema and may be as low as 50 beats per minute. Simultaneously, there is a characteristic diminution of the cardiac output^{131, 132, 176, 272, 273, 274, 275}, for which both the bradycardia and a diminished stroke volume can be held responsible. Since the reduction of the blood flow is sometimes more marked than that of the general oxygen consumption, an abnormally great arterio-venous oxygen difference has been found in some instances²⁷³. The gradual development of this phenomenon could be followed after total thyroidectomy in euthyroid patients⁴⁴. It furnishes another evidence against the teleological conception of a purposeful automatic adjustment of the circulation to peripheral oxy-

genous but not necessarily quantitatively parallel and are mutually independent within certain limits. Medication with thyroid hormone results in an increase of the stroke volume as well as of the minute volume²⁷³.

The total circulatory volume of myxedematous individuals tends to be below normal^{133, 134, 276, 277}, in keeping with a demonstrable diminution of the peripheral blood flow^{278, 279} which is particularly reduced in the vessels of the skin^{274, 275}. The low heat production and compression of the cutaneous vessels by the myxedematous swelling of the surrounding tissues have been considered as causal factors in this derangement of the blood distribution. The velocity of the blood flow is greatly reduced^{275, 276, 277, 278} as a result of the sluggish heart action.

Spurious and Genuine Congestive Heart Failure ("Myxedema Heart")

In many cases of advanced myxedema, a combination of impressive signs involving the heart makes its appearance, such as

(c) susceptibility of the apical impact; (d)

decreased voltage of the electrocardiogram. The fact that all these changes proved reversible under treatment with thyroid hormone, except in instances of co-existing heart pathology of a different nature, caused H Zondek in 1918²⁷¹⁴ to postulate a specific form of heart disease and to coin the term "myxedema heart". He interpreted its characteristic features as indicating true congestive cardiac failure. The symptomatology of "myxedema heart" was essentially confirmed by later observers^{927, 1027, 1746, 1972, 2140} in widely varying percentages of their respective series of observations. The classification of myxedematous cases with cardiac involvement in the categories of pure "myxedema heart", on the one hand, and of "arteriosclerotic heart disease" on the other, is of necessity rather arbitrary because of the high incidence of coronary sclerosis which prevails in myxedema as a peculiarity of this disease. Consequently, it is impossible in many cases, probably in the majority, to decide where the "myxedema heart" ends, where "arteriosclerotic heart disease" begins, and where both overlap. Nevertheless, a substantial number of cases presenting the above-outlined characteristics and, at the same time, differing sharply enough from the ordinary forms of arteriosclerotic heart disease and congestive heart failure, to be set aside as a definite morbid entity, can be isolated from the recorded series of "cardiac" myxedematous patients. They exemplify the more or less uncontaminated genuine "myxedema heart".

A deliberately schematic juxtaposition of some of the most important divergencies between the ideal form of "myxedema heart" and genuine congestive failure is given in Table 4. The elements of this comparison are largely based on the critical evaluations by Waring³⁵⁰² and Friedberg¹⁰⁰⁸. It would be of particular interest to obtain some information also regarding electrolyte behavior as well as adrenal cortical function in cases of pure "myxedema heart", compared with findings in plain, congestive failure, as these factors seem to be of fundamental significance in the origin and mechanism of the latter (p 490 ff, 496 ff).

From the enumerated differences, it appears quite clear that "myxedema heart" in the strict sense of the term is not identical with congestive cardiac failure and that it constitutes, in fact, its opposite in a number of important respects.

What then is the essence of this problematic myxedematous heart disease? Some authors^{1756, 1972} go so far as to declare that the "myxedema heart" is no heart disease at all, but merely "a manifestation of the disease myxedema". This extreme attitude was later mitigated by Means²²⁷⁵. Without entering into any dispute regarding the validity of the term "heart disease" for a condition which appears so very "cardiac", even though in an unusual sense, the writer agrees with the opinion of those who emphasize the fact that much of the symptomatology of "myxedema heart" is a masquerade

which fakes or at least exaggerates primarily cardiac alterations by means of primary non-cardiac mechanisms. The so-called enlargement of the heart is often merely a deceiving pericardial effusion (p. 155 ff.) which may be likewise responsible in part for some other seemingly cardiac abnormalities, such as the distant heart sounds, the weak apex beat, and the low voltage of the electrocardiogram¹⁷⁵⁶ (p. 153). The occurrence of pericardial effusion seems to be more common than generally suspected¹⁷⁵⁶. It is probably a result of the abnormal capillary permeability which forms a part of the myxedema syndrome^{1751, 1750} and which may also give rise to effusions in

TABLE 4

Comparison of the Characteristics of Congestive Heart Failure and of Typical "Myxedema Heart"

	CONGESTIVE HEART FAILURE	MYXEDEMA HEART
Venous pressure	Increased	Normal
Pulmonary congestion	Present	Absent
Hepatic congestion	Present	Absent
Dependent edema	Present	Absent or moderate
Orthopnea	Present	Absent
Tachycardia	Present	Absent
Circulatory volume	Increased	Decreased
Capillary permeability	Normal	Increased
Isolated pericardial effusion	Rare	Common
Protein content of serous effusions	Low	High
Basal metabolism	High	Low
Efficacy of digitalis	Good	Nil
Efficacy of diuretics	Good	Nil
Therapeutic efficacy of thyroid hormone	Nil	Good

other serous cavities and to the development of peripheral edema. The high protein content of the serous effusions of myxedematous patients^{1758, 1759} is to be explained on the same basis. The rapid disappearance of the effusive phenomena under thyroid treatment before normalization of the basal metabolism was taken as an indication of their dependence on a rather complete cessation of spontaneous thyroid activity¹⁷⁵⁴.

Whether the enlargement of the heart silhouette and the low voltage of the electrocardiogram can be ascribed to pericardial effusion exclusively appears doubtful, especially also in view of the post mortem findings of a myxedematous swelling of the heart muscle (p. 157).

One more phenomenon which has been observed by some^{1762, 1760, 1760, 1760}, but not by others¹⁷⁶¹, in myxedema and which may give the misleading

impression of established congestive heart failure, is a decrease of vital capacity. In the absence of pulmonary congestion, it may be due merely to a weakness of the respiratory muscles¹⁶⁰⁶.

The existence of a myxedematous heart does by no means constitute a complete protection against the simultaneous persistence or development of other forms of heart disease, especially of coronary and "hypertensive" heart disease, so that mixed clinical pictures may arise which include the features of real congestive failure, even pulmonary edema^{2140, 2141}. Means²²⁷¹ claims to have seen true congestive heart failure in myxedema only when another heart lesion was present. However, it is difficult, if not impossible, to draw the borderline of pathogenesis in the individual case from the criteria of clinical symptomatology alone.

Angina Pectoris

The occurrence of angina pectoris in patients with myxedema appears somewhat paradoxical in view of the often dramatic therapeutic results which have been achieved through total thyroidectomy and other induced forms of hypothyroidism in cases of existing angina pectoris. This apparent contradictoriness loses a good deal of its perplexity, however, if we consider the intrinsic and extrinsic factors which contribute to the development of the anginal syndrome. In the first place, it must be emphasized that the majority of those myxedematous patients who do suffer from genuine anginal pains begin to feel these pains only if and when treatment with thyroid hormone is instituted^{5, 519, 1216, 1503, 1622, 2275, 2279, 3184}. In formerly euthyroid angina patients who had developed myxedema as a sequel of an otherwise more or less successful thyroidectomy³⁰⁵ or radio-iodine treatment¹⁰⁴⁰, the necessity to administer thyroid hormone proves not infrequently the source of a dilemma in that this substitutive therapy may be accompanied by a prompt return of the anginal symptoms^{305, 1040}.

Taken all in all, one may say that in the above-described categories of hypothyroid patients, the anginal symptoms are not caused by the deficiency or lack of thyroid function per se but, on the contrary, by the introduction of thyroid hormone into their system. The first group, those with spontaneous myxedema, can be considered as having been potential angina candidates because of the generally high incidence of coronary sclerosis in hypothyroidism (p. 157). Only the absence of the thyroid hormone, i.e., the lack of activation of their adrenergic catecholamines, had protected them from the anoxiating, pain-producing effects of these amines (p. 373) until the latter were put into action by the artificial application of thyroid hormone. The second group, those with artificially induced myxedema, were ex-angina patients, still retaining their sclerotic coronary arteries, but benefited by a relaxing inactivation of their ever-present

adrenergic catecholamines, due to the removal of the activating thyroid, until the ability of their adrenosympathogenic neurohormones to produce hypoxia was re-instituted by thyroid medication.

Cases of spontaneous myxedema in which genuine angina pectoris develops before thyroid treatment^{190, 219, 222, 223, 224} are not common. Yet, considering the otherwise angina-preventing effectiveness of the hypothyroid state, they appear more numerous than one would expect, were it not for the well-known arterio-sclerosis-promoting capacity of myxedema. The assumption of a disproportionately high incidence of coronary sclerosis in this disease is borne out by the autopsy reports concerning myxedematous patients who had died from myocardial infarction^{217, 218, 192, 225, 214}. Thus, both factors which are decisively responsible for the exaggerated acute chemical myocardial hypoxia, the cause of anginal pain, may be present in a high percentage of myxedematous individuals: (1) coronary sclerosis which reduces coronary reserve to such an extent that even subnormal adrenergic action can bring about intense painful hypoxia, (2) artificial administration of thyroid hormone which will reactivate the adrenergic neurohormones to full anoxiating efficiency, possibly even in the presence of normal coronary arteries: angina pectoris factitia.

Finally, there remain those rare and problematic cases of alleged angina pectoris in myxedematous persons whose pains are reported to have disappeared under thyroid therapy^{122, 127, 131, 221}. Friedberg¹²⁰ points out that no satisfactory explanation is available for such events, but he expresses skepticism regarding the correctness of the diagnosis in those cases. Neuralgic and myalgic pains are a very common feature of hypothyroidism and may easily give rise to misinterpretations.

Electrocardiographic Changes

No endocrine disorder is associated with *electrocardiographic changes*.

...the *QRS* complex is not quite as regularly seen as the *P* and *T* changes, but it occurs often as a very impressive phenomenon. The above-named electrocardiographic findings, as well as *sinus bradycardia*, were confirmed by numerous observers^{124, 125, 126, 210, 226, 214, 222}.

Deviations of the electrical axis are frequently present in enlarged myxedematous hearts. The *P-Q* interval may be considerably prolonged^{120, 211}.

Partial atrio-ventricular block has been recorded by several workers^{211, 214, 263, 269}. The Q-T is occasionally shortened¹⁷⁵⁶, extrasystoles and intra-ventricular conduction disturbances occur in isolated instances²¹⁰.

Complete or partial normalization of the above-mentioned electrocardiographic signs can be induced within a few weeks by adequate medication with thyroid hormone^{2140, 2275, 2369, 2717}. However, a prolonged P-Q interval and inverted T-waves, especially in leads I, V₂ and V₄⁷⁸⁴, may persist in those cases in which coronary sclerosis is significantly involved. In hypertensive patients, abolition of the myxedema may even tend to bring a previously masked inversion of the T-wave²²⁷⁵ to the fore. Axis deviations will revert to normal²²⁷⁵ unless fixed by other co-existing conditions.

The causes of the electrocardiographic alterations of the myxedematous heart are only partially understood. The bradycardia is due in all likelihood to the deficient activation of the acceleratory intrinsic catecholamines within the heart muscle. The prolongation of P-Q, unless due to coronary sclerotic lesions of the conduction system, may well be ascribed to a preponderance of vagal tone on the same basis of adrenergic inactivation.

The low voltage of P, T and QRS is not, as originally believed, a result of impaired conduction by the skin. This was convincingly proven by the fact that insertion of needle electrodes under the skin or in the veins did not produce significantly different electrocardiographic tracings³⁵⁹. The low metabolism per se cannot be made responsible, as other types of hypometabolism were not found to be associated with similar electrocardiographic changes²⁷⁶⁵. It is of interest that the most striking normalizations of the low voltage seem to occur in those cases in which the shrinkage of the cardiac silhouette is most marked²²⁷⁵ and that withdrawal of fluid from the pericardial sac may be immediately followed by an improvement of the electrocardiogram which it might have taken at least several days to achieve by hormone treatment¹⁷⁵⁶. These observations, appear strongly suggestive of an important role of the insulating mantle of pericardial effusion in reducing the electrocardiographically demonstrable portion of myocardial voltage. This assumption is supported by the experimental diminution of electrocardiographic voltage through intrapericardial injection of fluid^{1709, 2973}. It seems improbable, however, that pericardial effusion alone should be responsible for the low voltage of the myxedematous electrocardiogram, as believed by some investigators¹⁷⁵⁶. Tapping of the pericardial sac fails to restore the ECG to complete normalcy, and the presence of myxedematous swelling of the myocardium in advanced cases (p 157) lends positive support to the contention^{207, 1980} that short-circuit effects and dissipation of the action current take place within the myocardium and the other myxedematous tissues which are interposed between heart and registering electrodes.

The frequent occurrence of coronary sclerosis in myxedematous individuals undoubtedly accounts for the inversion of the T-wave in many instances. Hypoxia, due to anemia may serve as another contributing factor in some.

Electrocardiographic changes in infantile cretins resemble those of adult myxedematous patients in most salient points. They respond promptly to thyroid medication and were ascribed chiefly to myocardial involvement²⁷⁰⁵.

Roentgenographic Changes of the Heart

Apart from characteristically *sluggish, worm-like pulsations* with a minimal excursion of its margins, the cardiac silhouette of myxedematous individuals is distinguished by a *diffuse rounded enlargement* which concerns all chambers and which can be considered as being present in the majority of all classical cases of myxedema. Since Zondek's first description²⁷¹¹, it has been recorded by many observers^{28 197, 656 198, 1561, 1756, 2146, 2770, 2771}.

According to Means²⁷²¹, the diameter of the heart shadow was found one cm or more greater than the half diameter of the chest in 34 of 48 cases; in 22 cases it was five cm or more greater than the half diameter of the chest. Occasionally the heart silhouette assumes enormous proportions. The fact that thyroid medication almost invariably induces its shrinkage to a normal

reported case of co-existing hypertension, the enlargement of the cardiac silhouette failed to disappear²⁷²⁴. It is worthy of note that in some instances of total thyroidectomy in euthyroid cardiac cases the fluoroscopic heart shadow grew larger despite an improvement of the clinical cardiac status²⁷⁰². Another significant point which militates against a participation of true congestive failure in many myxedematous patients with large heart shadows is the lack of visible pulmonary congestion, even in the presence of unilateral or bilateral pleural effusion²⁷⁰².

A definite settlement of the argument regarding the origin of the above-described roentgenological enlargement of the heart silhouette is made difficult by the fact that only relatively few untreated cases have come to autopsy and that even fewer are to be expected. One factor which is likely to contribute to an actual increase in size of the heart shadow is a myxedematous swelling of the myocardium. This, however, cannot possibly suffice to explain the marked enlargements which are so often seen. Neither can mere cardiac dilatation be accused of producing the more striking fluoroscopic pictures, although a moderate degree of dilatation of the flabby myx-

edematous heart muscle¹¹⁷⁰ may be present in some instances¹²¹⁹. Exclusion of genuine hypertrophy and of dilatation as decisive elements in the major enlargements of the heart silhouette, plus the demonstration of the presence of free fluid in the pericardial sac of numerous cases of myxedema^{1041, 1216, 1376, 1721, 1754, 1591, 1971, 2140, 3502} (Fig. 19) make it practically certain that pericardial effusion forms the principal if not the only factor which is to be held responsible for the characteristic radiological appearance of the myxedema heart. Kern and associates¹⁷³⁶, who have furnished additional electrocardiographic evidence for this conception (p. 154), suggest that the roentgenological terminology should be adjusted to the actual situation by speaking

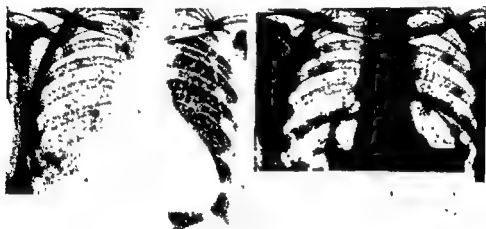


Fig. 1
a case of
Zdarsky
Vienna, 1910,

pericardial effusion in

of the "pericardial" rather than the "cardiac" silhouette, at least in referring to the myxedematous heart

Morphological Cardiovascular Changes

In keeping with the experimentally demonstrated facility with which arteriosclerotic lesions can be produced in the arteries of thyroidectomized animals (p. 39), arteriosclerosis is said to be a common feature in hypothyroid patients^{160, 352, 404, 939} and to occur even at a young age^{352, 1442, 1497, 2214, 2218, 2532}. The hypercholesterolemia of the myxedema syndrome, although certainly not the primary cause of atheromatosis, can be assumed to contribute to its development by furnishing the material supply for intimal lipid deposition (p. 245). Autopsy records of myxedematous individuals, especially of untreated ones, are not plentiful; but the prevalence of arteriosclerotic vascular lesions in the cases examined appears all the

more suggestive. Coronary arteriosclerosis with myocardial infarction has been observed in several autopsied cases^{202, 219, 220, 211, 229, 237, 213, 207}, including some of a young age^{235, 243}.

The appearance of the heart muscle is described as pale, flabby and sometimes as dilated^{202, 219, 229, 213, 247}. Although the term "hypertrophy" was used in several instances^{217, 227, 202}, there is good reason from histological evidence to doubt the existence of a real hypertrophy^{102, 226} and to interpret the increase in size and weight of the heart as being due rather to myxedematous swelling of the myocardial muscle fibers^{207, 262, 199, 229, 247}. Necrotic foci and fibrotic changes were occasionally seen^{202, 219, 202, 211, 229}, probably as a result of coronary sclerosis.

Treatment

The goal of hormone therapy in myxedema, as Means²²⁵ expressed it, is the "maximum possible well-being" of the patient. This seemingly commonplace statement needs emphasis because too vigorous efforts toward a fast and radical abolition of certain objective signs of myxedema, such as the low basal metabolism, puffiness of the skin, etc., may lead and have led to catastrophic developments.

The chief dangers arise from the cardiovascular system. They concern both the provocation of anginal symptoms which may end in fatal myocardial infarction, and the appearance of cardiac failure. In rare instances, even a cerebral vascular accident may be precipitated¹⁰². Furthermore, it can happen that a case of "pituitary myxedema" (p. 177), which involves hypofunction of the adrenal cortex, be mistaken for ordinary myxedema.

* * * * *

... .. an acute and possibly fatal crisis¹⁷⁴

In order to avoid disturbing confusion, oral thyroid medication should be based exclusively on the dosage of U. S. P. thyroid (dried powdered gland with an average 0.2 per cent iodine content). Whatever brand be used, its quantitative relationship to the U. S. P. standard should be ascertained and calculated in every instance. For some unknown reason the U. S. P. system of

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It has been pointed out by Means²²⁵ that there exists a rather fixed relationship between the amount of U. S. P. stand...

... .. of the nature of

... .. attempts to define clearly the amounts administered in terms

of uniform standards. According to Means²²⁷⁵, an initial dose of about 60 mg U. S. P. thyroid can be considered as safe for uncomplicated cases, but the patient must remain under careful supervision and the dosage may have to be halved or temporarily withdrawn if untoward side effects occur. Within a period of about two months, the daily dose may be gradually raised to 100-200 mg. If and when a sufficiently effective and well-tolerated amount has been determined, it may be established as a more or less permanent maintenance dose.

In patients older than 50 years, and particularly in those giving a history of angina pectoris or displaying objective signs of arteriosclerotic cardiovascular disease and hypertension, the administration of thyroid hormone has to be carried out with greatest caution and with smaller initial doses than those mentioned above. In such cases, a daily amount of 15-30 mg has been recommended for the beginning^{1610, 3352}, but even a dose of 6 mg has been seen to elicit severe anginal attacks so that it had to be reduced to 3 mg. Obviously such small quantities will be inadequate to abolish the myxedema completely, but this disadvantage must be accepted if grave complications are to be avoided. A compromise on a basal metabolic rate of say minus 25 per cent may be more rewarding than attempts to enforce a smaller figure. With the progress of general clinical improvement, the tolerance for the thyroid hormone tends to increase, and maintenance doses not much lower than those customary in uncomplicated cases may be reached²¹⁴¹ by gradual increments of about 8-15 mg each.

McGavack²¹³⁸ stresses the necessity to reduce the dosage under the following conditions: Appearance of anginal distress, a persistent decrease of the systolic blood pressure of more than 10 mm of mercury, a narrowing of the pulse pressure, a sudden increase of the heart rate of 20 or more beats per minute, symptoms of cardiac failure.

As far as the value of basal metabolism determinations for the estimation of clinical progress under hormone treatment is concerned, it should be kept in mind that congestive failure per se can elevate oxygen consumption so that the readings obtained may be misleading²¹⁴¹. Neither do weight, pulse rate, or circulation time seem to constitute reliable criteria in myxedematous patients with congestive failure²¹⁴¹. McGavack²¹⁴¹ advocates the determination of blood cholesterol and of capillary permeability (Lange's fluorescein method¹⁹¹²) instead, because of their specificity and sensitivity to thyroid function.

Although digitalis is said to be in general poorly tolerated by myxedematous patients²²⁷⁵, and although it is useless as a remedy for the symptoms of the pure "myxedema heart", it should be administered whenever the presence of true congestive heart failure warrants it³⁵⁹³, along with diuretics, etc. Morphine, is contra-indicated in myxedema^{2275 3352}

Heuristic Aspects of the Hypothyroid Cardiovascular Syndrome

Evaluation of the mechanisms by which the characteristic cardiovascular disturbances of the hypothyroid state are initiated in the individual case is sometimes made difficult by the fact that changes which concern the heart muscle directly and those which affect it secondarily by favoring the development of coronary sclerosis, overlap to a considerable extent. Thus, paradoxical clinical manifestations may occur, notably anginal symptoms, despite the otherwise angina-inhibiting effect of thyroid under-function.

However, in the majority of cases, the uncomplicated myocardial functional alterations of hypothyroidism and their hemodynamic sequelae dominate the clinical picture: bradycardia, diminished stroke volume, diminished total cardiac output, and diminished velocity of the blood flow. All of these form the diametrical counterparts to the outstanding cardiovascular features of thyrotoxicosis which we have ascribed to the well-known potentiation of adrenergic effects on the heart. Obviously the lack of thyroid hormone is apt to be associated with the opposite situation, namely, a marked inactivation of the effects of intrinsic adrenergic neurohormones upon the myocardium. The decreased cardiovascular efficiency of injected epinephrine and nor-epinephrine in athyroid animals and humans (p 31, 35, 399) corroborates this concept.

The low voltage of the electrocardiogram is believed to be caused mainly by the accumulated fluid inside and around the myocardium.

If the writer's hypothesis of an obligatory mediation of the calorigenic effects of the thyroid hormone through the ubiquitous adrenosympathogenic catecholamines is correct, the low basal metabolism of myxedema could likewise be explained as the expression of a loss of effectiveness of these calorigenic amines, in contrast to the

connection as . . . performance in muscular work, the energy cost for an equal amount of work was found subnormal in myxedema¹⁴; in other words, the oxygen consumption proved more economical than normal. Favorable as this arrangement may prove to be for the individual case of hypothyroidism, . . . granted to

human race mentioned authors would like to have it, for by the same token the thyrotoxic multitudes are afflicted with exactly the opposite phenomenon. Should one conclude that the latter deserve such discrimination or imply that Providence is unfair toward them?

Applied to the problem of angina pectoris, the principle of cardiac oxygen conservation in hypothyroidism accounts probably for the comparative rarity of anginal symptoms in untreated patients, even in the presence of coronary sclerosis (as also exemplified by the disappearance of angina

of uniform standards. According to Means²⁷⁵, an initial dose of about 60 mg U. S. P. thyroid can be considered as safe for uncomplicated cases, but the patient must remain under careful supervision and the dosage may have to be halved or temporarily withdrawn if untoward side effects occur. Within a period of about two months, the daily dose may be gradually raised to 100-200 mg. If and when a sufficiently effective and well-tolerated amount has been determined, it may be established as a more or less permanent maintenance dose.

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thyroid treatment, especially in elderly patients and in those with pre-existing asymptomatic coronary sclerosis. Congestive failure can likewise be induced by injudicious dosage of thyroid preparations.

Under cautious hormonal treatment, all cardiovascular signs and symptoms which are directly caused by thyroid deficiency can be brought to disappearance. Co-existing congestive heart failure requires in addition the usual therapy with digitalis, etc.

The functional features of the genuine myxedema heart and its hemodynamic effects can be largely explained on the basis of impaired efficiency of the intrinsic adrenergic neurohormones in the heart, due to the lack of the activating thyroid hormone. The stimulating cardiovascular effects of injected epinephrine are markedly reduced in myxedematous individuals.

There exist indications of a decreased adrenal cortical activity in hypothyroid patients, especially in cases of pituitary myxedema.

after thyroidectomy in euthyroid patients with established coronary sclerosis). Conversely, the easy provocation of angina even by a therapeutic dosage of thyroid hormone seems to be due, at least in part, to the high incidence of asymptomatic coronary sclerosis in myxedema. The behavior of the anginal syndrome in relation to spontaneous and induced atherosclerosis and to thyroid treatment furnishes valuable clues for the understanding of the joint thyroid-adrenergic chemical mechanism of ordinary angina pectoris and for the rationale of its therapeutic approaches.

The fact that vascular lesions of the kidneys do not constitute a part of the myxedema syndrome²²⁷⁶ seems to be compatible with the writer's hypothetical assumption that such lesions be largely dependent on the quantity and toxicity of adrenosympathogenic catecholamines which pass through the kidneys in the process of their excretion.

General vascular lesions in myxedema belong to the atheromatous type, which is promoted by hypercholesterolemia, rather than to the arterio-sclerotic variety, which seems to be produced essentially by the combined action of adrenal corticoids and adrenosympathetic catecholamines (p. 245, 252). This state of affairs is consistent with the low sympathetic activity and probably low adrenal cortical function in hypothyroidism. The latter is suggested by the finding of a diminished excretion of 11-oxy corticosteroids in myxedematous patients, which was restored to normal by thyroid medication³³⁴⁴, and by a diminished eosinopenic response to epinephrine injection⁷⁸.

Summary

The syndrome of the so-called "myxedema heart" which represents the primary effects of thyroid deficiency on the cardiovascular system consists of (a) sluggish heart action with bradycardia and diminution of stroke volume, minute volume, and velocity of the blood flow; (b) a diffuse enlargement of the roentgenographic heart silhouette which is caused by swelling of the heart muscle, probably some degree of dilatation, and often pericardial effusion, (c) low voltage of the ECG, frequently accompanied by inversion of the T-wave. Congestive failure is not a constituent of the syndrome of uncomplicated "myxedema heart".

True congestive heart failure with increased venous pressure, pulmonary and hepatic congestion and dependent edema may accompany hypothyroidism as a result of pre-existing heart disease or may supervene due to the development of arteriosclerotic heart disease which is promoted by the hypercholesterolemia of myxedematous individuals. The blood pressure may be low, normal, or high, the latter independently of the hypothyroid state.

Angina pectoris is rare in untreated myxedema but appears readily under

17-ketosteroids and glucocorticoids in some cases^{167, 168} corroborates this conception.

The presence of goiter was stated in 25 per cent and 52 per cent respectively in two series of 72⁶⁷ and 166^{67, 69} cases of acromegaly, but although signs suggestive of hyperthyroidism are often observed^{67, 117}, they do not necessarily coincide with an enlargement of the thyroid. Biopsy of removed, seemingly toxic thyroid glands from acromegalic individuals failed to reveal the expected histological characteristics of thyroid overactivity⁶⁷. Some functional observations which militate against a prominent involvement of hyperthyroidism in the acromegalic syndrome will be discussed on p. 166.

Atrophy of the gonads is a frequent occurrence and has been reported in more than one-half of a series of acromegalic cases¹¹⁸, but it does not seem to be an integral part of the hormonal pattern of acromegaly, as evidenced by the high ketosteroid excretion in some cases¹⁴⁴. It was ascribed to mechanical injury to the rest of the pituitary gland, caused by pressure of the expanding eosinophil adenoma¹²².

In exceptional instances, there may be a simultaneous increase of both eosinophil and basophil elements¹¹⁸ and, accordingly, mixed syndrome with traits of both acromegaly and pituitary basophilism (p. 170). A few cases of acromegaly are said to have originated on a traumatic basis¹⁶⁷ and some develop after thyroidectomy¹⁶⁷. The thymus was found enlarged in 63 out of 115 cases⁶².

General Symptomatology; Diagnosis

The characteristic appearance of the acromegalic face with the plump, enlarged "acra", nose, jaw and cheek bones, producing a hexagonal frontal outline, and with protrusion of the superciliar arches, is so well known that it usually permits the diagnosis at first glance. The frontal teeth are often separated by interspaces, hands and feet assume a clumsy shape through widening of the fingers and toes; the chest expands in all directions, the thoracic spine becomes kypholordotic, appositional bone growth is roentgenologically visible on practically all parts of the skeleton, including the calvaria, and the pneumatic spaces appear greatly enlarged. Hypertrophic arthritic changes are a common occurrence.

The tongue becomes heavy and unwieldy, which may affect the speech. The skin is thick, tough and dry. Not infrequently it displays hypertrichosis. Obesity is only rarely seen in acromegaly.

Sexual activity may be temporarily increased in males in the earlier stages of the disease, and full-term pregnancy with normal childbirth is not impossible¹⁷⁰, but sooner or later the sexual functions are impaired.

The term "splanchnomegaly" is applied to enlargement of the internal organs which keeps pace with the growth and size of the whole body. The

Pituitary-Hypothalamic System

Acromegaly, Gigantism

Acromegaly and gigantism are widely considered as essentially the same disease, namely an over-production of the growth hormone by the eosinophil cells of the anterior pituitary lobe, but with the one difference that gigantism would represent the juvenile form, leading to excessive longitudinal growth; whereas acromegaly, appearing at a more advanced age after closure of the epiphyseal interspaces, would manifest itself rather by appositional growth and splanchnomegaly. The situation is probably not quite as simple as that. Acromegaly, with or without gigantism, has been seen occasionally in children¹⁶⁷⁸, but for practical purposes, the customary interpretation may be acceptable. A considerable overlapping of both syndromes exists, however, according to the statistical statement²²⁷⁰ that about 40 per cent of all giants (i.e., persons taller than 1.90 meters) show acromegalic traits and that about 20 per cent of all acromegaly patients are giants.

The symptoms of acromegaly were described by Pierre Marie in 1886 and recognized as a disturbance of pituitary function. Its occurrence is divided equally between male and female individuals and the disease is said to start in the majority of cases in the age group from 20-30 years¹⁶⁷⁹.

Endocrine Pathology

As a rule there is a benign eosinophil adenoma of the pituitary anterior lobe, but malignant adenomata are also occasionally seen. In rare instances, acromegaly may be produced by a pharyngeal tumor of hypophyseal tissue¹⁹⁷ or by a plain diffuse increase in number of the eosinophil cells²²¹.

Although the presumable origin of the growth hormone in the eosinophil cells is not directly proven with complete certainty, there are various indications which make it most probable and a leading role of the growth hormone in the development of the syndromes of acromegaly and gigantism can be considered as well established.

In view of the strategic position which the pituitary gland occupies within the endocrine system, it is not surprising that acromegaly is not infrequently associated with morphologically demonstrable changes in other endocrine glands. An actual increase in size of the adrenal glands has been reported in many instances^{626, 922, 2260, 2493}; the occasionally encountered hypertrichosis was interpreted as suggesting adrenal cortical hyperfunction¹⁶⁹, and the finding of a markedly augmented urinary excretion of both

tension in such cases¹⁵⁵. On the other hand, several observers comment on the infrequency of hypertension in acromegaly^{153, 223, 209}. Systolic blood pressure readings of less than 120 mm Hg were reported in 28 per cent²⁴³ and 30 per cent⁶⁷ respectively. Even hypotensive levels were seen in some cases^{164, 113}. An unusual lability of the blood pressure with paroxysmal elevations may be present occasionally^{153, 109}. Altogether, it can be said that arterial hypertension is not a characteristic constituent of the acromegalic syndrome (Table 5), but its occurrence seems to be promoted to some extent by either the hormonal action of the eosinophil tumor or possibly by some mechanical effect exerted by it upon the blood supply and the trophic state of the adjacent anterior pituitary tissue.

TABLE 5
Blood Pressure in Different Forms of Pituitary Pathology
(After A. Ruggieri²²³)

STATUS OF PITUITARY GLAND	NUMBER OF CASES	AVERAGE AGE	SYSTOLIC BLOOD PRESSURE			
			Maximal	Minimal	Average	"Normal" average of corresponding age group [*]
Basophil adenoma	23	29	300	95†	180	120
Acromegaly	24	45	270	104	142	140
Simmonds' disease	42	42	155	50	80	136

* Calculated from several statistical publications

† Measured shortly before death from septicemia.

Heart Enlargement and Failure

In view of the "splanchnomegalic" trend toward a general enlargement of the internal organs in acromegaly, a proportionate hypertrophy also of the heart is to be anticipated, but radiographic and post mortem evidence (p. 167) indicates that beyond this the hearts of acromegalic individuals (in contrast to those with gigantism^{1049, 2113}) are often very much larger than such a mere participation in general tissue growth would warrant^{810, 154, 3270} (see Fig. 75).

The pathological nature of these cardiac enlargements is further demonstrated by the high incidence of congestive cardiac failure and cardiac death which usually concludes the case history of acromegalic patients^{93, 1026, 110, 220}, unless they fall victims to diabetic coma or intercurrent infections. The average age of onset of cardiac failure in acromegaly has been given as 42 years¹⁶ and the average age at death from this cause as 48 years⁶⁷. In Courville and Mason's⁶⁰ series of 24 cases, 18 had cardiac failure and six died from it. The clinical manifestations of congestive heart failure in

sometimes disproportionate hypertrophy of the heart will be discussed on p. 167. Frequently the massive appearance of acromegalic and gigantic individuals is not paralleled by commensurate physical strength, a fact which has furnished the background to many tales of ancient folk-lore.

Carbohydrate metabolism is frequently disturbed in acromegaly. Diabetes has been reported in 33 per cent⁹² to 40 per cent²²² of the cases. It appears usually as a later complication, on an average nine years after onset of the acromegalic symptoms³⁴⁹, and seems to be due to an insensitivity to insulin rather than to a lack of this hormone¹⁵⁰².

The urinary excretion of uric acid⁹⁴⁵, creatine¹⁵⁵ and creatinine³⁰³⁰ may be increased.

Certain peculiarities of the mental state in acromegaly may be explained on the grounds of self-consciousness of the patients because of their appearance, but beyond that these individuals are characteristically quiet, slow, and usually good natured.

Bitemporal hemianopsia, caused by pressure of the hypophyseal tumor upon the chiasma of the optic nerves, has been reported in 32 per cent of a large series of cases⁹².

Gigantism develops usually during the teen-age years. Since rapid and extensive longitudinal growth is often caused by other conditions than hypophyseal tumors, the differential diagnosis may create a problem, unless facial changes of the acromegalic type, x-ray findings and sexual disturbances point clearly toward the pituitary.

The most decisive criterion for an intrasellar tumor of the pituitary is an enlargement of the sella turcica with a depression of its bottom, pseudo-elongation and thinning of the dorsum sellae and usually well-preserved, protruding anterior clinoid processes. The planum sphenoidale and the anterior wall of the sella form a sharp angle

Blood Pressure

Reports on the blood pressure in acromegaly are rather contradictory. The question of presence or absence of hypertension in this disease is of

patients vary between 10 per cent¹⁵⁵, 30 per cent¹⁴⁹ and 50 per cent¹. These discrepancies may be explained in part by the fact that the occurrence of hypertension differs according to sex and age groups. It was found to be most common in women beyond the 40th year (60 per cent)³³², as contrasted with an only 11 per cent incidence in men of the same series. The

hypertension in acromegaly has been suspected as being involved in the mechanism of hyperbasophil cells of the pituitary has been suspected as being involved in the mechanism of hyper-

tension in such cases¹⁵⁵. On the other hand, several observers comment on the infrequency of hypertension in acromegaly^{155, 228, 2091}. Systolic blood pressure readings of less than 120 mm Hg were reported in 28 per cent¹⁵⁵ and 30 per cent⁶⁷³ respectively. Even hypotensive levels were seen in some cases^{161, 1448}. An unusual lability of the blood pressure with paroxysmal elevations may be present occasionally^{155, 1448}. Altogether, it can be said that arterial hypertension is not a characteristic constituent of the acromegalic syndrome (Table 5), but its occurrence seems to be promoted to some extent by either the hormonal action of the eosinophil tumor or possibly by some mechanical effect exerted by it upon the blood supply and the trophic state of the adjacent anterior pituitary tissue.

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acromegaly do not differ significantly from those seen in cases of ordinary "hypertensive" or coronary heart disease. Dyspnea appears at an early stage.

Syncope is a common phenomenon, but not necessarily related to cardiac failure^{803, 1026, 3270}. Whether it is in any way precipitated by the frequent presence of varicosities of the leg veins^{155, 167} and by pooling of blood in the legs, in accordance with the observations of Chapman and Asmussen⁵⁰⁵, cannot be decided at this time.

Electrocardiographic Changes

In keeping with the common structural and functional abnormalities of the acromegalic hearts, the ECG is only rarely found normal, even in clinically not far advanced cases. The abnormalities consist of left axis deviation, intraventricular conduction disturbances, depression of S-T, changes of the T-wave, especially in the later stages, and arrhythmias^{155, 603, 1449}. They do not display any characteristics which would seem specific for acromegaly *per se* but they rather show the ordinary pattern of so-called "hypertensive" heart disease, regardless of the presence or absence of hypertension.

In consideration of the frequent occurrence of hypermetabolism in acromegaly (p. 167), a thyrotoxic influence upon the heart was thought of as a possibility, but closer scrutiny made this appear improbable¹⁵⁵.

Thyroid Involvement and Basal Metabolism

A rather intimate association of acromegaly with hyperthyroidism was originally suspected because of the frequent presence of goiters⁶³⁰ as well as of hypermetabolism in acromegalic individuals²¹²⁷ (p. 167). However, there seems to be much less of a connection between the enlargement of the thyroid and the elevation of the basal metabolism in acromegaly than one might expect. The two phenomena appear quite independently of each other, with a greater frequency of occurrence of hypermetabolism, as compared with that of goiter. In fact, according to the observations of Cushing and Davidoff⁶³⁷, in 75 per cent of those cases which had an elevated metabolism, the thyroid was not enlarged. On the other hand, the biopsy of some goiters showed no histological signs of hyperthyroidism⁶⁷³ and neither thyroidectomy^{603, 680} nor propyl-thiouracil^{142, 2127} nor iodine⁶⁰³ proved efficient in depressing the hypermetabolism. Studies with radioactive tracer iodine-uptake did not reveal any indications of increased thyroid activity³⁵⁶⁹, even in cases with hypermetabolism²¹²⁷. Some authors claim that a certain degree of hypothyroidism actually exists more frequently in acromegaly than thyrotoxicosis⁵⁰. Outright myxedema has been observed in acromegalic women after the menopause¹⁵⁵.

In contrast to the lack of positive evidence of true hyperthyroidism as being a characteristic side feature in acromegaly, there still remains the fact of a definite hypermetabolic tendency in many acromegalic patients. According to one statistical compilation²⁴⁹, the basal metabolism of 50 per cent of a series of acromegalic persons was higher than 10 per cent; in another series²⁵⁰ 54 per cent of the cases had an elevated metabolism with an average of plus 18.6 per cent and a maximal reading of 61 per cent. From all these findings, the conclusion was drawn that the hypermetabolism in acromegaly must be caused by other factors than by an over-active thyroid^{183 251 252}. The isolation from the pituitary of a metabolism-stimulating

TABLE 6

Incidence of Arteriosclerosis and of Adrenal Cortical Hyperplasia or Atrophy Respectively in Cases of Hyper- and Hypofunction of the Pituito Adrenocortical System (After A. Ruggieri²⁵³)

STATUS OF PITUITARY GLAND	NUMBER AND AGE OF CASES		NUMBER OF CASES WITH ARTERIOSCLEROSIS (% OF GROUP)	DEGREE OF ARTERIOSCLEROSIS (% OF GROUP)			ADRENALS (% OF GROUP)		
				Ab-sent	Slight or medium	Se-vere	Normal	En-larged (lipid rich)	Atro-phic
Basophil adenoma	25	38	100	0	72	28	37	63	0
Diffuse increase of basophils	8	55	100	0	37	63	—	—	—
Acromegaly	26	49	77	23	61	16	34	62	0
Total	59	47	90	10	63	27	37	63	0
Hypopituitarism	24	58	58	42	50	8	22	5	73

principle which was found active also in thyroidectomized animals²⁴⁸ and which is neither identical with the growth hormone nor with the thyrotrophic hormone may prove an important step toward an explanation of the interesting phenomenon of non-thyrogenic hypermetabolism in acromegaly as well as in other conditions.

Morphological Cardiovascular Changes

An early development of arteriosclerosis has been emphasized by various observers^{182 184 187 188 192} as a rather common event in acromegaly (Table 6). Renal arteriosclerosis and "chronic interstitial nephritis" are likewise found in the majority of instances²⁴⁹. Some authors mention a general dilatation of the blood vessels and particularly of the aorta in both acromegaly and gigantism^{182 184 189 191 276}.

Hypertrophy of the heart is the most conspicuous cardiovascular anomaly

in the acromegalic syndrome. While it is said to remain approximately within the limits of general body growth in gigantism^{1992, 3715}, it may by far transcend these proportions in acromegalic patients. The hypertrophy which concerns as a rule exclusively or prevailingly the left ventricle^{155, 2593}, may assume enormous dimensions so that heart weights of 1,140 grams, 1,200 grams⁶⁰³, 1,275 grams²⁴⁴⁵ and 1,300 grams¹⁶⁰¹ have been recorded. Dilatation and flabbiness of the myocardium is mentioned in some instances²⁵⁹³.

As far as the microscopic findings in the heart are concerned, there is a certain dissension of opinions. Some observers claim that the individual muscular fibers are greatly enlarged⁶³⁶, while this is denied by others⁶⁰³. Fragmentation, cellular infiltration, and fibrosis are rather uniformly reported, however^{603, 636, 1169}, and the similarity with so-called "hypertensive" heart disease appears maintained also in this respect.

Treatment

The indications for therapeutic activity in gigantism and acromegaly are, in part, determined by the progressiveness or quiescence respectively of the disease and by the acuity of danger for the eyesight, hence by both hormonal and mechanical considerations. The *surgical approach*, either through the opened calvaria^{632, 3010} or through the nasal cavity¹⁶¹⁹, is usually reserved for cases in which the relief of pressure on the optic chiasma is a primary concern. A more conservative procedure is the temporary implantation of radon-seeds into the sphenoidal sinus close to the tumor, or into the tumor itself²⁴⁵⁰. The method of choice for most cases in the progressive stage, however, consists of *X-ray irradiation* which is capable of bringing the process to a standstill^{1611, 1169, 3457} and even to restore a severely impaired vision¹⁶¹¹ (personal observation) through shrinkage of the tumor. A regression of the disfiguring somatic changes cannot be expected. In cases of accompanying diabetes, the insulin sensitivity may also be improved by X-ray therapy¹⁵⁰⁹. There is no specific hormonal treatment for acromegaly or gigantism in existence, although sex hormones may be of some limited usefulness^{1169, 3030}.

No statistical data are available concerning the effect of x-ray therapy upon cardiovascular developments, but disappearance of cardiac failure and of dyspnea⁶⁰³ and abolition of blood pressure lability¹³⁵ have been reported in individual cases. Otherwise, the treatment of cardiac failure in acromegaly is the same as that in "hypertensive" heart disease and other related forms of congestive failure.

Heuristic Aspects of the Acromegalic Cardiovascular Syndrome

The marked genuine cardiac hypertrophy which develops in acromegalic patients rather regularly, even in the absence of hypertension, is of interest

for the evaluation of the pathogenesis of hypertrophic states of the myocardium in general, including the so-called "hypertensive" heart disease (p. 457) and the so-called "idiopathic" cardiac hypertrophy (p. 443). The customary mechanistic interpretation of cardiac hypertrophy as being caused solely by the "load" or "burden" of a high blood pressure, is obviously not applicable to the normotensive cases with huge hearts. Consequently, attempts were made to "explain" the phenomenon as occurring "to compensate for the growth of the patient", as being "an attempt of the heart to meet the stage of diminishing cardiac reserve", etc. Such nebulous phraseology simply feigns to solve a biological problem by conveniently shifting it into the realm of mystical teleology where arguments are easy to invent.

In reality the heart hypertrophy in acromegaly serves as a convincing example of the hormonal chemical basis of the process of cardiac enlargement. The hormone or hormone combination which is responsible for this reaction of the heart muscle cells is not yet clearly known, but the recent observation²⁰⁴ that the pituitary growth hormone, combined with DCA, produces a marked, disproportionately large hypertrophy of the heart in the absence of hypertension, seems highly significant. In the preceding chapter we discussed instances of marked cardiac hypertrophy in cases of pheochromocytoma and of adrenal cortical tumors. Their morphological, electrocardiographic and functional characteristics were identical with those of the hypertensionless hypertrophic heart of acromegaly, and we shall again encounter the same cardiac situation in the cases of so-called "hypertensive" heart disease and of "idiopathic" cardiac hypertrophy (pp. 457 and 443). The relationships between these different alternatives are still obscure in most details but in considering the striking analogies, we begin to perceive the outlines of functional patterns which seem to be composed of a varying interplay of action between (a) the adrenosympathetic hormones, apparently

which in acromegalic individuals may constitute an analogy to the nephrosclerosis, produced experimentally by the administration of growth hormone (p. 48).

The non-thyrogenic hypermetabolism of acromegaly is reminiscent of that observed in pheochromocytomas and suggests a possible involvement of the calorogenic adrenergic neurohormones in the cardiac complications of acromegaly.

Summary

The outstanding cardiovascular feature of the acromegalic syndrome is the often enormous hypertrophy of the heart, mainly of the left ventricle, and its ultimate development into fatal congestive cardiac failure. The

structural, electrocardiographic, and functional peculiarities of the acromegaly heart are identical with those of so-called "hypertensive" heart disease, except that hypertension is often entirely absent.

Goiters are frequently seen in acromegalic and gigantic patients, but they are usually not toxic and the tendency toward an elevated basal metabolism seems to be due to other factors.

Arteriosclerosis and vascular kidney lesions are common features in acromegaly.

The non-hypertensive hypertrophy of the heart occurring in acromegaly is of importance for the evaluation of the problem of cardiac hypertrophy and failure on a hormonal chemical basis, as contrasted with current mechanistic conceptions.

Pituitary Basophilism (Cushing's Disease)

The term "Cushing's disease" or "pituitary basophilism" is reserved for those cases of "Cushing's syndrome" (p. 90) in which a basophil adenoma or a diffuse increase of basophil cells in the anterior lobe of the pituitary gland is either demonstrable at autopsy or suggested by radiological signs which indicate the presence of a tumor within the sella turcica.

The obvious existence of a relationship between pituitary basophilism and the development of Cushing's syndrome is of considerable interest for the problem of interference of the pituitary in adrenal cortical activity and thus of its indirect interference in cardiovascular function and structure.

Endocrine Pathology

In his classical description of the syndrome named after him, Harvey Cushing⁶³⁹ (1932) based his conclusion of its causation by "pituitary basophilism" upon the reports of three autopsied cases with basophil adenomas, which had been published by the writer²⁶⁴⁵ (1924), by Parkes Weber²⁵²⁹ (1926) and by Teel³³⁶⁰ (1931) respectively. Later compilations of cases^{1759, 3340} revealed the not infrequent absence of significant morphological changes of the pituitary. The types of structural abnormalities which were found in the anterior lobe proved rather manifold. They include a diffuse increase of the basophil cells without adenoma, eosinophil adenomas, chromophobe adenomas, even a complete absence of basophil cells¹⁰¹⁸. This irregularity of findings, together with the fact that basophil adenomas are relatively frequently present in the pituitary gland without engendering any clinical symptoms^{597, 3321}, made the original conception of an exaggerated secretory activity of the basophil cells as the cause of Cushing's disease doubtful. Crooke⁶¹⁵ and others^{1120, 2743, 3340} observed that the most characteristic morphological correlate of Cushing's syndrome in the pituitary is not the change in number or topical arrangement of the basophils, but a peculiar and ap-

parently specific "hyalinization" of these cells. This seems to facilitate an understanding of some of the puzzling contradictions. It suggests a degenerative involvement²⁹⁹ instead of the previously suspected secretory over-activity of the basophil cells, but it does not offer any positive explanation of the mechanism by which these qualitative cellular changes in the pituitary are linked with the adrenal cortical hyperfunction which is directly responsible for the symptoms of Cushing's syndrome (p. 90).

activity in Cushing's disease. It cannot be accepted as definite proof, however, as long as an increased production of ACTH by the pituitary has not been unequivocally demonstrated in these cases. Earlier claims regarding the presence of increased amounts of adrenocorticotrophic hormone in the serum and urine of Cushing cases¹⁶³ have been questioned by other workers who found a low adrenocorticotrophic activity in the serum and none in the urine of such patients^{296d, 297}.

Heinbecker^{143b, 146b, 147} assumes on the grounds of both pathological and experimental observations of his own that the adrenal cortical hyperfunction in Cushing's disease is caused by a primary degenerative or atrophic alteration of the paired paraventricular nuclei of the hypothalamus which would lead to a secondary degeneration and functional impairment of the basophil cells. This would entail a prevalence of the eosinophils to which he ascribes adrenocorticotrophic properties. This hypothesis is difficult to reconcile with the absence of the characteristics of the Cushing syndrome in the great majority of cases of acromegaly and gigantism which are generally attributed to eosinophil hyperfunction. The observation of degenerative changes in the hypothalamus following experimental treatment with ACTH and cortisone makes it appear more probable that the hypothalamic findings of Heinbecker are secondary and induced by adrenal cortical over-activity⁴⁹¹.

Finally there remains the possibility that some of the hypophyseal changes found in Cushing's disease might constitute a response to primary adrenocortical hyperfunction^{173a, 215f}. Adrenal cortical hyperplasia frequently coincides with pituitary basophilism^{174b, 267a, 218f, 299} (Table 6, p. 167) and the question as to where the primary disturbance is located must be left in suspense for the time being.

General Symptomatology; Differential Diagnosis

Attempts have been made to differentiate Cushing's disease from the primary . . . symptom . . .

were claimed to exist were not confirmed by subsequent, more extensive observations^{1678, 1759}. In view of this state of affairs, the reader is referred to p. 95, concerning the symptomatology of Cushing's disease, as it can be considered as practically identical with that of Cushing's syndrome.

The most specific criterion of the presence of a pituitary adenoma, basophil or other, within the sella turcica, is a radiologically demonstrable erosion of the anterior wall of the sella with replacement of the soft wavy outline of the limbus chiasmatis and tuberculum sellae by a more or less sharp angle. This detail does not seem to be widely appreciated, even among radiologists, and is therefore represented in Figure 20. According to the literature, positive x-ray findings proving an intrasellar adenoma were recorded only in a minority of verified cases of Cushing's disease^{178, 2274, 2637, 3046}, but it might well be that the above-mentioned sign was overlooked

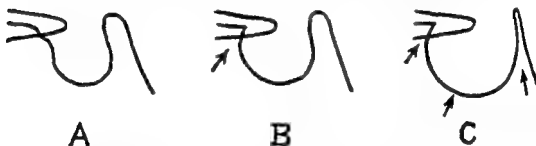


FIG. 20 Outline of sella turcica. A normal, B small tumor of the anterior lobe of the pituitary, C large intrasellar tumor

in some of them. It has served the writer in making the clinical diagnosis of a very small tumor of the anterior lobe in the case which was later incorporated in Cushing's paper, and also in another case of pituitary basophilism. Because of the smallness of the adenomas, bitemporal hemianopsia occurs only rarely (in 3-4 per cent of the cases)¹⁶⁸⁷.

The bioassay for the adrenocorticotrophic hormone of the pituitary has not yet been developed to the point of clinical applicability. The excretion of 17-ketosteroids with the urine is said to be more markedly increased in cases of primary adrenocortical adenoma, as compared with classical Cushing's disease⁶¹⁶.

Cardiovascular Manifestations

Arterial hypertension with marked elevation of both the diastolic and systolic pressures is an almost invariable characteristic of Cushing's disease as well as of Cushing's syndrome and what has been said on p. 97 with regard to the latter applies to both conditions.

The same holds true for the very frequent occurrence of cardiac hypertrophy, congestive heart failure and arteriosclerotic lesions⁴⁷⁷ (see also Table 6)

Treatment

Roentgen irradiation of the hypophysis proved amazingly successful in a limited number of patients^{619, 1369, 1441, 1759} in whom all abnormal somatic and functional signs and symptoms disappeared, including the hypertension. Despite its ineffectiveness in other cases^{397, 1044}, it has recently again been recommended with more optimism²⁰⁹⁷. The implantation of radon seeds into the pituitary gland was effective in a case of Cushing's syndrome which had not responded to estrogens and to x-ray therapy but became normalized after this treatment for a period of nine years. Other forms of hormone therapy are mentioned on p. 101. Careful avoidance of infections is advisable in Cushing's disease because of the great susceptibility of these patients to septic complications^{819, 1349, 1677, 1749, 2437}, and vigorous antibacterial measures must be taken in such emergencies.

Heuristic Aspects of the Pituitary Basophilic Syndrome

If we could be certain of the correctness of any one of the theories which ascribe to the pituitary a leading part in the development of Cushing's disease, either through secretory over-function of the basophils or through degenerative under-function with resulting eosinophil preponderance, much would be gained also regarding the question of pituitary involvement in the origin of arteriosclerosis, of essential hypertension and of congestive heart failure. However, as matters stand at the present time, it must be admitted that we do not even know whether the morphological changes of the pituitary which are encountered in Cushing's syndrome may be regarded as the expression of primary lesions, giving rise to adrenal cortical over-function through an excessive production of the adrenocorticotrophic hormone, or whether they are merely secondary reactions to spontaneous hyperadrenocorticism. The provocation of the Cushing syndrome through ACTH administration on the one hand, and the occasional spectacular normalizing effects of irradiation of the pituitary gland on the other, tend only to confirm the familiar fact that the adrenal cortex can be influenced by the pituitary anterior lobe; but they do not prove the pathogenic primacy of the pituitary in the syndrome of "pituitary basophilism". If and when accurate methods for the assay of ACTH in body fluids and tissues will become available, the heuristic value of Cushing's disease will probably be greatly increased.

Summary

Cushing's disease (pituitary basophilism) is pathogenically closely related to, if not identical with, the basophilic syndrome.

Whether

the pri-

mary or secondary feature of the condition remains an open question. The symptoms of pituitary basophilism

were claimed to exist were not confirmed by subsequent, more extensive observations^{1678, 1759}. In view of this state of affairs, the reader is referred to p. 95, concerning the symptomatology of Cushing's disease, as it can be considered as practically identical with that of Cushing's syndrome.

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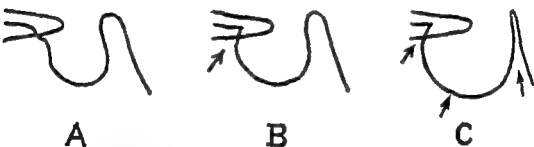


FIG. 20 Outline of sella turcica. A normal, B small tumor of the anterior lobe of the pituitary, C large intrasellar tumor

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The bioassay for the adrenocorticotrophic hormone of the pituitary has not yet been developed to the point of clinical applicability. The excretion of 17-ketosteroids with the urine is said to be more markedly increased in cases of primary adrenocortical adenoma, as compared with classical Cushing's disease⁶¹⁶.

Cardiovascular Manifestations

Arterial hypertension with marked elevation of both the diastolic and systolic pressures is an almost invariable characteristic of Cushing's disease as well as of Cushing's syndrome and what has been said on p. 97 with regard to the latter applies to both conditions.

The same holds true for the very frequent occurrence of cardiac hypertrophy, congestive heart failure and arteriosclerotic lesions⁴⁷⁷ (see also Table 6).

tary in such instances as being precipitated by an insufficient blood flow and multiple thrombus formation in the gland following acute blood loss were shaped at a time when modern concepts of pituitary-adrenal endocrine reactions to the stress of severe hemorrhage had not yet been evolved. The genuine, verified type of Simmonds' disease is almost twice as common in women as it is in men. It develops, as a rule, during adult life and is but rarely seen to begin before the tenth year or after the 65th year^{191, 192}. A special variety of the disease seems to be the one which appears frequently in unmarried young women with delayed puberty¹⁹³.

Among the cases in which the pituitary anterior lobe was found more or less intact, there are some in which autopsy disclosed an interruption of the hypothalamic-pituitary pathways and fluid channels by tumors or other destructive lesions affecting the pituitary stalk or the bottom of the third ventricle^{123, 116, 131, 194}. Increasing indications of a neurohumoral control of anterior pituitary function by hypothalamic centers (p. 45) seem to give some support to the opinion of those investigators who ascribe the clinical syndrome in such cases to interference with the cerebral regulation of pituitary activity^{123, 193, 134}. Where no gross anatomical abnormalities could be detected at all, one might think of a primary derangement within those hypothalamic centers which seem to be responsible for the functional state of the pituitary, and in particular for the development of cachexia^{142, 210}.

Although no definite proof is yet available for this latter assumption, it would form a reasonable link between the classical cases of Simmonds' disease and their symptomatological counterpart of the "anorexia nervosa" type, in which a clear-cut morphological substrate in the region of the diencephalic-hypophyseal system seems to be entirely lacking. Certain clinical differences between the classical Simmonds' syndrome and that of psychogenic anorexia nervosa do exist and will be discussed on p. 176, 177. The clinical picture of anorexia nervosa includes many endocrine features of a pattern very similar to that of panhypopituitarism. In the individual case the borderlines are often so hazy that it appears difficult to disclaim any involvement of psychically induced functional alterations of the pituitary²¹².

The condition of the other endocrine organs outside of the damaged pituitary is characterized by a state of atrophy of the adrenal cortex (Table 6, p. 167), gonads and thyroid^{213, 214} which used to be designated as "multiple endocrine glandular sclerosis"¹⁹⁵ before the dominating role of the pituitary had been recognized. The clinical manifestations resulting from these endocrine deficiencies are undoubtedly caused indirectly by the inability of the pituitary to elaborate and secrete its various glandotropic hormones. The distribution of these functional changes throughout the

and hyperadrenocorticism are clinically indistinguishable, except for occasional radiological signs produced by a sellar tumor.

The cardiovascular manifestations of pituitary basophilism (hypertension, cardiac hypertrophy, congestive heart failure, arteriosclerosis, nephrosclerosis) are probably essentially due to adrenal cortical over-activity and may be interpreted in the same way as in the section on hyperadrenocorticism (p. 102).

Radiation treatment of the pituitary proves dramatically effective in some cases but fails completely in the majority. Various hormone applications (estrogens, testosterone, parathyroid hormone) may also achieve normalization, but their results are likewise unpredictable.

Panhypopituitarism; Anorexia Nervosa; Pituitary Myxedema

The syndrome whose causal connection with atrophy of the anterior lobe of the pituitary was recognized by Simmonds³¹⁴⁵ in 1914, seemed at first easy enough to define as a result of the general break-down of anterior pituitary function. However, it soon became clear that matters were more complex, that the classical syndrome may develop in the absence of any demonstrable anatomical lesion of the pituitary, and that there exists a very similar, apparently psychosomatic syndrome ("anorexia nervosa") whose pathogenic relation to the pituitary is not yet fully clarified. With these limitations in mind, we shall discuss both the genuine pituitary form of Simmonds' disease and its related psychogenic homologue under the all-inclusive term of "panhypopituitarism", because a probable secondary involvement of pituitary function may be assumed even in the latter syndrome. "Pituitary myxedema", which constitutes a special variety of panhypopituitarism, will also be discussed in this section.

Endocrine Pathology

The types of lesions which are capable of destroying the anterior pituitary to such an extent that serious functional impairment or complete loss of function will develop are manifold, such as traumatic injuries through fracture of the skull, hemorrhages, bacterial abscess formation, tuberculosis, syphilitic gumma, primary benign or malignant tumors, metastases, cysts, thromboses, infarctions, and finally plain atrophy without any identifiable cause^{1677, 1879, 2058}. It is significant that in a comparatively large number of females the clinical syndrome makes its appearance at varying time intervals after parturition, especially if a great loss of blood and shock had been connected with it^{577, 899, 1697, 2784, 3111}. A temporary predisposition of the pituitary for necrotic changes during its rapid puerperal involution appears possible^{2784, 3109}. Earlier views which regarded the destruction of the pitui-

pathogenic background only in the latter. The differential diagnosis is of some prognostic and therapeutic significance. It may be facilitated by a comparison between the two groups, point by point, as given by Escamilla and Lasser²⁹⁵. Indications in favor of true Simmonds' disease are: (1) in women, onset post-partum, especially if it was complicated by excessive hemorrhage and collapse; (2) onset following a severe infection; (3) radiologically discernible alterations of the sella turcica or calcification foci within its cavity; (4) loss of axillary and pubic hair; (5) premature senility; (6) atrophy of the breasts in females, (7) complete or almost complete absence of 17-ketosteroids from the urine^{1929, 2336}; (8) eosinophilia; (9) glucogenic corticoids low or not at all detectable in the urine²⁴⁴²; (10) male sex; (11) non-response to psychotherapy and slow response to hormone treatment (p. 180). On the other hand, features which occur with approximately equal frequency in both syndromes are: cachexia, loss of sexual function, asthenia, hypometabolism, hypotension, bradycardia, gastrointestinal disturbances. Anorexia nervosa occurs about nine times more frequently in women than in men.

Even more important from a practical point of view is the clinical identification of *pituitary myxedema* and its separation from primary hypothyroidism, because of the acute danger of precipitating a possibly fatal Addisonian crisis if thyroid medication is administered without preceding adequate adrenal cortical substitutive therapy (p. 181). The clinical appearance of these patients can be quite deceiving^{149, 1822, 1973, 2277} and it may be good policy to regard any case of myxedema as being of pituitary origin until this assumption has been disproved. Points of some differential diag-

nosis are usually ^{1929, 2336} normal or low blood cholesterol^{1929, 2336}, eosinophilia, lymphocytosis, low 17-ketosteroid excretion in the urine, radiological signs of a pituitary tumor. History of onset after ¹⁹ , no im-

usually not too difficult, on account of the more marked and differently distributed pigmentation, the more prominent electrolyte derangement, the less depressed basal metabolism, and the less conspicuous loss of weight in the latter. The urinary excretion of 17-ketosteroids, water soluble corticoids and glucocorticoids ^{1929, 2347, 2567}, but ¹⁷ ,
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endocrine system may display certain quantitative variations. In the case of so-called "pituitary myxedema", with marked atrophy of the thyroid gland, the hypothyroid signs over-shadow all other features of endocrine inadequacy.

Occasionally occurring instances of spontaneous destruction, or of therapeutic surgical removal of the pituitary anterior lobe^{898, 1678} without resulting cachexia suggest that the latter may require some diencephalic participation in order to develop.

General Symptomatology; Differential Diagnosis

The general clinical symptomatology of the classical form of Simmonds' disease, as well as of its varieties, especially also of "anorexia nervosa", has been represented by Escamilla and Lissner⁸⁹⁹ in an extremely thorough statistical study which covers practically the entire extensive literature on this subject until 1942. All essential details may be found in this review and we can confine ourselves to a brief enumeration of the salient and most common signs and symptoms: Loss of weight, although a prominent feature and often leading to extreme emaciation, may nevertheless be of a minor degree only in about one-third of the cases. Loss of libido and of sexual function and general asthenia are practically always present. Yet, pregnancies have been recorded in a few exceptional cases^{899, 3110}. In women, the breasts are usually atrophic. Young individuals may show signs of early senility³³⁷⁴. Axillary and pubic hair is scarce or entirely missing. The skin is dry. A gray brownish discoloration of the integument is often seen but does not attain the degree of Addisonian pigmentation. The temperature is often subnormal. Cold temperature is poorly tolerated. The teeth are subject to decay and may fall out. Moderate or marked fasting hypoglycemia, increased glucose tolerance, increased insulin sensitivity, and a high eosinophil count point toward glucocorticoid deficiency. A deeply depressed basal metabolism which may fall to levels as low as -60 per cent, in conjunction with a slight elevation of the blood cholesterol level, reveals accompanying thyroid underfunction, even in the absence of conspicuous signs of myxedema. The serum electrolytes seem to remain within normal limits, as a rule⁸⁹⁹, but some instances of low serum sodium concentrations have been reported^{2153, 2326}. The response to the Cutler, Power, Wilder sodium deprivation test^{2389, 3265} and the beneficial effect of salt administration in some cases (p. 181) are clearly indicative of disturbances in the electrolyte metabolism of the hypoadrenocortical pattern. Cardiovascular manifestations will be discussed on pp. 178-180.

Anorexia and emotional disturbances are phenomena which both genuine Simmonds' disease and the syndrome of anorexia nervosa have in common in many cases, but states of emotional imbalance seem to form the actual

pathogenic background only in the latter. The differential diagnosis is of some prognostic and therapeutic significance. It may be facilitated by a comparison between the two groups, point by point, as given by Escamilla and Lasser²⁴³. Indications in favor of true Simmonds' disease are: (1) in women, onset post-partum, especially if it was complicated by excessive hemorrhage and collapse; (2) onset following a severe infection; (3) radiologically discernible alterations of the sella turcica or calcification foci within its cavity; (4) loss of axillary and pubic hair; (5) premature senility; (6) atrophy of the breasts in females; (7) complete or almost complete absence of 17-ketosteroids from the urine^{197, 238}; (8) eosinophilia; (9) glucogenic corticoids low or not at all detectable in the urine²⁴³; (10) male sex; (11) non-response to psychotherapy and slow response to hormone treatment (p 180). On the other hand, features which occur with approximately equal frequency in both syndromes are: cachexia, loss of sexual function, asthenia, hypometabolism, hypotension, bradycardia, gastrointestinal disturbances. Anorexia nervosa occurs about nine times more frequently in women than in men.

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normal or low blood cholesterol^{269, 266}, eosinophilia, lymphocytosis, low 17-ketosteroid excretion in the urine, radiological signs of a pituitary tumor, history of onset after pregnancy with hemorrhage²⁷³, weight loss²⁷³, a small heart²⁷³, no improvement or even deterioration under thyroid therapy alone²⁵³.

The differentiation between panhypopituitarism and Addison's disease is usually not too difficult, on account of the more marked and differently distributed pigmentation, the more prominent electrolyte

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not occur

the 17-ketosteroid output with the urine within 24 hours. During the subsequent 48 hours, 10 mg ACTH are administered every six hours. During the second 24 hours of this 48 hour period, urine is again collected and the 17-ketosteroid output determined. The normal increase in adults is approximately 4-8 mg per day³³⁹⁸.

The ACTH and epinephrine eosinopenia tests yield subnormal results in both panhypopituitarism and Addison's disease, and can therefore not be used for differentiation between the two conditions²⁷⁵⁴.

Some exceptional cases of panhypopituitarism develop by spontaneous transition from obesity to emaciation⁹⁷².

The duration of Simmonds' disease extends over a very wide range, between a few months and several decades^{1679, 2760}.

Blood Pressure

Although there is a definite tendency toward *arterial hypotension* in both classical Simmonds' disease and anorexia nervosa, not only normal but even slightly hypertensive blood pressure levels have been observed in a minority of cases^{2153, 2236}. Ruggieri²¹⁹² recorded hypotensive readings in 66 per cent of 48 cases. Escamilla and Lissner⁶⁹³ subdivided their statistical material in 101 verified and 158 unverified cases of Simmonds' disease and 20 cases of anorexia nervosa. The respective blood pressure values of these three groups are given in Table 7. They do not reveal any significant differences between the behavior of the blood pressure in the primary hypophyseal and the probably "psychogenic" cases. Escamilla and Lissner⁶⁹³ were inclined in 1942 to attribute the arterial hypotension in the cases of anorexia nervosa to malnutrition rather than to an endocrine functional deficiency. Considering newer concepts of starvation as a stress situation with profound secondary involvement of the endocrine system, we do not see any point in trying to discriminate sharply between such alternatives. Under-nourishment per se can elicit degenerative changes in the anterior lobe of the pituitary²³⁹⁴ and functional alterations of the adeno-hypophyseal-adrenocortical system on a psychogenic emotional basis have been concluded from a drop in the circulating eosinophils¹⁶⁹². It appears probable, therefore, that the hypotension of both genuine Simmonds' disease and anorexia nervosa occurs in principle in a similar manner as that existing in primary hypoadrenocorticism (p. 112). A significant deficiency of mineralocorticoids was detected in patients with hypopituitarism by the results of salt secretion tests^{2516, 3261}.

A paradoxical fall of the blood pressure, provoked by muscular exercise, was observed by several workers in patients with signs of hypopituitarism^{1931, 2971, 2972, 3054, 3261}. This phenomenon could be partially or completely abolished by treatment with anterior lobe extracts. Change from recumbent

to erect position was also found to be accompanied by a precipitous fall of blood pressure, sometimes to indistinguishably low levels^{194, 197, 197, 213}. Similar reactions may occur in Addison's disease^{211, 215} and in states of malnutrition²¹⁶, the latter probably also due to induced adrenal cortical insufficiency. The underlying mechanism is possibly the same which weakens, e.g., the carotid sinus reflex²¹² and the pressor response to cerebral ischemia²¹³ in adrenalectomized animals, namely sodium depletion of the cardiovascular contractile cells and consequently a diminished reaction to thepressor stimuli of the adrenosympathetic neurohormones. It must be

responsible for such unusual electrolyte changes as low serum electrolyte

TABLE 7
Blood Pressure in Simmonds' Disease and Anorexia Nervosa
(After Escamilla and Lissner²¹⁴)

DIAGNOSIS	BLOOD PRESSURE					
	Maximal		Minimal		Average	
	Systol	Diastol	Systol	Diastol	Systol	Diastol
Simmonds' disease						
(a) Verified cases	160	100	50	40	96	62
(b) Unverified cases	142	100	60	0	91	61
Anorexia nervosa	108	82	72	40	80	50

levels, combined with an increase of intracellular sodium and decrease of intracellular potassium, as observed in two cases, one of which had a moderate arterial hypertension^{215, 216}. Alterations in the carbohydrate metabolism of the cardiovascular cells, caused by a deficiency of adrenal glucocorticoids, may be another factor in depressing vascular responsiveness to sympathogenic nor-epinephrine (p. 29).

Cardiac Manifestations

Marked bradycardia of 60 beats per minute or less is quite frequently present in cases with both Simmonds' disease (21 per cent)²¹⁷ and anorexia nervosa (31 per cent)²¹⁸. It has to be attributed in all likelihood to the secondary thyroid deficiency of the hypopituitary syndrome and to its desensitizing effect regarding the accelerating adrenosympathetic neurohormones on the heart muscle (pp. 35 and 399). Heart rates higher than 60 are often seen but outright tachycardia hardly ever occurs. In one case of

anorexia nervosa the cardiac output was found normal in relation to the patient's ideal weight²³¹⁷.

The *electrocardiogram* of patients with hypopituitarism is not frequently mentioned in the literature. It was either found normal²¹⁸⁴ or it displayed a low voltage^{663, 2109, 2427} with prolonged P-R²¹²⁷ and R-T²²⁵² intervals. These findings are well compatible with a deficiency of thyroid hormone. Left axis deviation with shifting pacemaker and periods of cardiac standstill were recorded in one case as an exceptional observation²¹⁵³.

The usual radiographic smallness of the heart^{1677, 2252} corresponds to a lack of adrenal corticoids, possibly also of pituitary growth hormone (p 49).

Morphological Cardiovascular Changes

In a series of 21 autopsied cases in which findings concerning the heart were available²²⁹², smallness and atrophy are mentioned in 27 per cent and brown discoloration in 36 per cent.

In 24 cases with an average age of 58 years, no arteriosclerotic lesions were found in 42 per cent. Among the remaining cases, only 8 per cent showed arteriosclerosis of a major degree, probably acquired before onset of the pituitary deficiency. This relatively low incidence of arteriosclerotic changes in hypopituitarism contrasts sharply with a group of 59 cases with overfunction of the hypophyseal-adrenocortical system (pituitary basophilism, acromegaly) of a younger average age (47 years) in which 90 per cent had arteriosclerosis, with a severe degree in 27 per cent (Table 6, p. 167).

Treatment

Except for the psychogenic cases of functional hypopituitarism and anorexia nervosa in which spontaneous recovery takes place²¹⁸⁴, or in which *psychotherapy* alone proves successful, the foremost therapeutic goal in panhypopituitarism is either the effective substitution of the various glandotrophic functions of the pituitary anterior lobe through adequate pituitary replacement, or a direct substitution of the secondarily deficient functions of the atrophic adrenal cortex, thyroid and gonads individually.

The first alternative has frequently proven unsuccessful in the past because of a lack of accurately standardized *pituitary preparations*. Although excellent results were achieved with genuine anterior lobe extracts in a considerable number of cases¹⁶⁷⁹, others remained unimproved, possibly in part because of inadequate dosage. Surprisingly, implantation of fresh calf glands was also often followed by remarkable improvement or normalization^{231, 1880, 2312, 3297} which persisted for one year or more. A definite conclusiveness of these results was doubted by some workers because of the possibility of purely psychogenic effects^{1678, 2257}. Recent experiences with

pituitary implantations which yielded impressive but only transient results according to other criteria³⁶³ make lasting effects of this form of treatment unlikely. Many clinicians prefer the somewhat cumbersome but more flexible and, in general, more promising administration of adrenal cortical preparations (p. 118 ff.) with or without extra salt, plus thyroid hormone (p. 157) and testosterone^{363, 371, 383, 386, 387}, the latter in the form of implanted pellets (150-300 mg), intramuscular injections (25 mg twice a week), as methyl testosterone linguets by mouth (10 mg daily) or any combination of these. The dosage must be carefully adjusted to the needs of the individual case, as estimated from its symptomatologic pattern and in compliance with clinical response. Points to be considered in particular are: (a) the necessity to maintain an adequate proportion between thyroid and adrenocortical medication^{377, 387} because over-dosage of the former without sufficient adrenal cortical support might precipitate a state of severe hypoadrenocorticism, especially in cases of pituitary myxedema; and (b) a limitation of the testosterone dosage in females in order to avoid undue masculinization. With general clinical improvement, the blood pressure, basal metabolism, and serum electrolytes return to normal^{377, 387} under such a combined treatment.

ACTH, although representing only the adrenocorticotrophic function of the pituitary, proved of great therapeutic value in cases in which a deficiency of this vital function dominated the clinical picture (3-10 mg every 6-12 hours)^{170, 386}. The way in which the patient responds to the therapeutic administration of a standard dose of 10 mg of ACTH^{386, 387, 388}

improvement will occur in the latter.

Heuristic Aspects of the Hypopituitary Cardiovascular Status

The state of the cardiovascular system in patients with hypopituitarism is of interest insofar as it reflects the simultaneous, even though incomplete deficiency, of both the

cortical
elaboration
blood press
system to a

and exercise requirements. Regulatory sympathetic neurosecretory nor-epinephrine discharges, although in themselves probably unimpaired, seem to have become incapable of exerting their full pressor effect on vessel walls whose cells have become deficient in corticoid-retained sodium, and therefore less responsive to neurohormonal contraction stimuli. Bradycardia and low pulse pressure, on the other hand, are to be ascribed to the insufficient sensitization of the heart muscle

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way as in adult cases of panhypopituitarism, the syndrome of pituitary dwarfism will result. Intracellular tumors which cause the syndrome belong usually in the category of chromophobe adenomas. Suprasellar tumors or diencephalic neoplasms may either destroy the hypothalamic centers which are necessary to maintain normal pituitary function²²¹ or interrupt the communication between the hypothalamus and the pituitary⁴⁴, or they may exert an injurious pressure upon the gland itself. Their diagnostic recognition is often facilitated by the presence of radiologically visible calcifications within the tumor mass, deformation of the sella turcica and the signs of increased intracranial pressure. On the other hand, there exist cases of plain atrophy of the pituitary^{277 286 287}. Under these circumstances, the sella turcica may appear unusually small^{286 264}.

Atrophy of the adrenal cortex is occasionally seen but does not constitute a regular feature of pituitary dwarfism. The adrenals were even found enlarged in some cases²⁹³.

Clinical Symptomatology

Pituitary dwarfism differs from other types of growth retardation by the inevitable presence of two specific criteria, namely (a) marked genital hypoplasia with lack of pubic and axillary hair and under-developed breasts, although not always with complete absence of sexual function; 17-ketosteroid excretion of 0 or almost 0¹⁰⁸, (b) lack of ossification of the epiphyseal interspaces which may remain open until advanced adult life.

In accordance with the varying degrees of involvement of the diencephalon and of the thyrotropic and adrenocorticotrophic hormones of the pituitary, there is either moderate obesity or conversely thinness, even emaciation, the latter sometimes combined with a peculiarly wrinkled senile appearance of the skin ("geroderma"). Myxedematous signs may further complicate the picture. A poor resistance to infections of the

... occurring at an age, e.g., 63¹⁰⁷ and 91 years²⁸³. The intelligence is usually intact.

In a few cases of dwarfism, diabetes mellitus was observed¹¹⁸, but the pituitary origin of these particular forms of growth impairment has been questioned³⁰².

Cardiovascular Manifestations

In a group of eight cases, compiled by D. — — — 1965.

to its epinephrine-nor-epinephrine content because of diminished thyroid secretion. The very low basal metabolic rates seem likewise to indicate an impaired calorogenic activity of the adrenergic neurohormones due to under-function of (a) the catecholamine-activating thyroid and (b) the adrenal corticoids which, in turn, are necessary to maintain thyroid metabolic efficiency. Cardiac atrophy points likewise toward a deficiency of adrenal corticoids and possibly of pituitary growth hormone. The generally low incidence of arteriosclerosis in hypopituitarism may be in part attributed to the under-function of the adrenal cortex. The accompanying hypothyroidism, on the other hand, could account for the development of arteriosclerosis of the large vessels which is found in some of the cases.

The participation of the cardiovascular system also in the syndromes of psychogenic functional hypopituitarism and anorexia nervosa of presumably hypothalamic origin brings up the question as to whether a deficiency or inactivation of the cerebral vasopressor and heart-stimulating amine enkephalin is in any way involved in the hypotension and bradycardia of hypopituitarism. As long as the physiological functional role and possible entry into the blood stream of enkephalin has not been established, it seems premature to speculate on this problem; but it should be kept in mind for future investigation.

Summary

Hypopituitarism, caused either by structural lesions or by psychogenic and hypothalamic functional inactivation of the pituitary, leads to secondary trophic regression and functional deficiency of the adrenal cortex, thyroid gland, and gonads. Inadequate elaboration of the adrenal corticoids seems to cause arterial hypotension, supposedly through sodium depletion and metabolic alterations of the cardiovascular contractile cells; accompanying hypothyroidism accounts for bradycardia and low basal metabolic rate, probably through inactivation of cardioaccelerator and calorogenic catecholamines. The frequently observed atrophy of the heart is interpreted as a result of combined deficiency of both adrenal corticoids and the pituitary growth hormone. Treatment with hypophyseal preparations, especially ACTH, adrenal cortical extracts (DCA, cortisone), thyroid hormone and testosterone permits in most instances more or less complete recovery, including normalization of the cardiovascular status. Pituitary myxedema requires thyroid treatment with adequate adrenocortical support.

Pituitary Dwarfism

Endocrine Pathology

If lesions of the anterior lobe of the pituitary or of the adjacent diencephalic areas interfere with pituitary function during childhood in a similar

hormones involved. Such studies would be of particular interest in regard to the possible role of the growth hormone or its deficiency in cardiac structural alterations.

Summary

Cardiovascular anomalies (hypotension, hypertension, small and large hearts) seem to be irregularly distributed among cases of pituitary dwarfism. They require more systematic study before any pathogenic conclusions can be reached.

Adiposogenital Dystrophy (Fröhlich's Disease)

Adiposogenital dystrophy is a condition caused by partial hypothalamic-pituitary under-function due to tumors, hydrocephalus, cysts, encephalitis, and other local lesions. Its chief manifestations consist of obesity and sexual infantilism or, if the syndrome develops after puberty, regression of sexual function and of secondary sexual characteristics. Diabetes insipidus is not infrequently present as an accompanying symptom of hypothalamic-posterior pituitary origin.

Temporary retardation of sexual development with associated obesity is a rather common feature among young boys. It frequently gives way to normal conditions without treatment and although symptomatically similar, it is not identical with Fröhlich's disease. No systematically collected data concerning the cardiovascular system in such cases are available.

In a small series of mostly young patients with Fröhlich's disease, the blood pressure was found within normal limits^{23,24}. Among nine autopsied cases, there were two with apparently atrophic adrenals and one with cortical hyperplasia. The heart was described as small and flabby in one, enlarged in three. Arteriosclerosis was present in two cases of 55 and 64 years respectively.

These few data are not suggestive of any characteristic direct influence of the adiposogenital syndrome upon the cardiovascular system. This is not surprising in view of the fact that *none* of those hormones which exert significant specific effects on heart and blood vessels, namely adrenergic neurohormones, mineralocorticoids, the thyroid hormone and possibly the growth hormone, is regularly and profoundly involved in the endocrine pattern of adiposogenital dystrophy. No particularly informative observations concerning the cardiovascular system can be expected, therefore, from this syndrome.

No specific studies concerning heart size and function and concerning the electrocardiogram seem to be available. In a few cases, radiological smallness of the heart was recorded²³⁹².

Morphological Cardiovascular Lesions

Post-mortem findings of the heart reveal considerable discrepancies. In some cases, it was found small, in keeping with the small dimensions of the body^{1597, 2640}. On the other hand, an enlargement of the heart was stated in several instances^{2392, 3267}. Arteriosclerotic vascular lesions were observed in three out of eight autopsied cases²³⁹². Two of them presented nephrosclerotic changes, and one of these patients died from cerebral hemorrhage¹⁷¹⁷.

Treatment

Even though some successes of treatment with growth hormone have been reported^{467, 2963}, the therapeutic application of this hormone alone is not sufficient for normalization in the great majority of cases because of the wider range of pituitary functional impairment, which needs to be corrected. Testosterone^{3345, 3622} and estrogen³³⁴⁵, preferably in combination with chorionic gonadotrophins^{779, 3355}, proved to be particularly useful in that they not only remedy the sexual deficiencies and their sequelae, but also promote body growth within certain limits by inducing puberty. The most opportune age to begin treatment is the 11th or 12th year³³⁵⁵. Thyroid hormone by itself is ineffective, except in myxedematous cases, but may be administered together with sex hormone and, in case of adrenal cortical insufficiency, with corticoids.

Heuristic Aspects of the Cardiovascular Status in Pituitary Dwarfism

The available data concerning the cardiovascular system in pituitary dwarfism are scarce and difficult to interpret in relation to those hormones which are deficient in this syndrome. The apparently prevailing tendency toward a lower blood pressure and small heart agrees with the apparent secondary depression of adrenal cortical function which is also suggested by the extremely low or absent 17-ketosteroid excretion. On the other hand, hyperplasia of the adrenals and the occurrence of arterial hypertension as well as of enlargement of the heart are no impossibilities in pituitary dwarfism. It is not clear however from the reports whether these enlarged hearts were actually hypertrophic or only dilated or edematous, as in hypothyroidism. In any event, it would be desirable in further studies of pituitary dwarfism to include carefully collected clinical and autopsy data on the heart, ECG, blood pressure reactions, electrolyte metabolism, etc., in conjunction with the quantitative assay for the various

occasionally out of the hormonal turmoil of the climacteric state. Chemical or bioassay will then also yield abnormal results regarding the 17-ketosteroids, the 11-oxysteroids, the thyroid-stimulating hormone, and others.

General Symptomatology

Apart from the common cardiovascular manifestations which will be discussed in the subsequent sections, there are various neurovegetative phenomena which may make their appearance long before the actual menopause sets in, e.g., paresthesias in hands and feet, especially during the night and the early morning hours, sneezing spells, vertigo, sighing respiration^{18,17, 1602}, cold extremities⁶²¹ and excessive sweating^{621, 104}. Some of these seem to be caused by an over-activity of sympathetic neurosecretion. Virilizing changes, such as beard growth and deepening of the voice, are attributable to an increased formation of adrenocortical androgens. Obesity seems to be connected with the glucocorticoids, and arthritic signs of the hypertrophic type with some as yet undefined adrenal cortical derangement. Temporary psychic disturbances of all degrees, mostly of a melancholy depressive character, complete the picture in many cases and establish fleeting transitions between "organic" and "psychosomatic" troubles. The clinical picture which develops after artificial castration is qualitatively identical with that of the natural menopause but may take on more intense forms¹⁴⁸ because of the abruptness and completeness of ovarian inactivation.

Blood Pressure

The old question as to whether the comparatively frequent occurrence of arterial hypertension of the "essential" hypertension type during the age of the climacteric^{1272, 1416, 1559, 1931, 2206, 2514, 2662, 2911, 3066, 3297} bears any causal relationship to the endocrine situation of the menopause can be answered in the affirmative with a great deal of likelihood. This is substantiated by the apparent role of the endocrine system in the pathogenesis and the involvement of the menopausal endocrine set-up on the other. However, this relation seems to be a rather indirect one. The interest of the present study is in the question whether an elevated blood pressure is a symptom of the climacteric.

function in order to maintain the blood pressure with the effects of menopause.

The elevations of blood pressure in the climacteric years are usually lat-

ent. Hyper-

Gonads

The Menopausal Syndrome; Gonadal Dysfunctions

The term "menopausal syndrome" is generally applied to a protean combination of a variety of symptoms and signs which frequently, although not regularly, attend the cessation of ovarian function, provided that this occurs as the result of a primary involution or removal of the ovaries and not as a secondary complication of pituitary gonadotrophic deficiency².

Endocrine Physio-Pathology

The natural menopause, the actual cessation of menstrual bleeding, occurs between the 45th and 50th year as a rule. It should be understood, however, that the state of endocrine imbalance which is connected with this one conspicuous phenomenon and which accounts for the manifestations of the menopausal syndrome may extend over periods of years before and after the last menstrual hemorrhage^{1009 1010}. Besides, ovulation or menstruation may continue for some time independently of each other, so that the "menopause" in the strict sense of the word is not to be regarded as an absolutely reliable criterion of ovarian non-function³⁰⁷⁶. In the case of surgical castration or inactivation of the ovaries through x-ray, the situation is clearer, of course. Other forms of ovarian pathology, especially tumors and, more rarely, infectious inflammations, may likewise elicit disturbances of the menopausal type if they interfere seriously with ovarian endocrine activity.

The outstanding demonstrable hormonal anomalies during the spontaneous and the artificially induced menopause are: (a) the more or less abrupt partial or total disappearance of estrogenic steroids from the urine¹⁸⁶⁷, and (b) a marked increase of urinary elimination of pituitary gonadotrophins which can reach amounts 50 times higher than the normal excretion by sexually mature women³⁰⁷⁶ and which remains high for the rest of the individual's life¹⁶⁷⁸. Whatever clinical manifestations appear in connection with the menopause are probably not due to any one of the two above-named factors per se, but rather to the secondary rearrangement of other hormonal activities, especially on the part of the anterior pituitary, the adrenal cortex and the thyroid gland, which leads slowly and sometimes only incompletely to a new equilibrium of the post-menopausal pattern. Most of the variegated menopausal symptoms can be traced to the prevalent interference of one or another of the above-named endocrine glands. Some full-fledged endocrine syndromes, such as myxedema, thyrotoxicosis, acromegaly, Simmonds' cachexia, or the adrenogenital syndrome, emerge

occasionally out of the hormonal turmoil of the climacteric state. Chemical or bioassay will then also yield abnormal results regarding the 17-ketosteroids, the 11-oysteroids, the thyroid-stimulating hormone, and others.

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sists of a suddenly arising subjective sensation of heat ascending to the face and arms and is often followed by a cold sweat. It is accompanied by a transient reddening of the upper part of the chest, neck, and face, due to dilatation of the cutaneous vessels.

Flushing with chills was complained of by 95.2 per cent of a series of 1000 menopausal women¹⁴¹⁶. Its mechanism is not quite clear but it appears significant that in women in whom flushing occurs spontaneously, all its subjective and objective manifestations can be promptly evoked by intravenous injection of epinephrine^{1268, 1417}. In those women of the menopausal age who did not flush spontaneously, this reaction was lacking¹²⁶⁸, as also in other non-menopausal persons¹²⁶⁹. The only non-menopausal type of individuals who were seen to respond to epinephrine with flushing were some patients with thyrotoxicosis¹²⁶⁹. This does not imply that hyperthyroidism forms an integral part of the menopausal syndrome. In a group of women presenting the flushing phenomenon, the highest basal metabolic rate observed was only plus 12.5 per cent¹⁴¹². However, the above-mentioned findings as well as the accentuation of other cardiovascular reactions to epinephrine in both menopausal¹⁴¹⁷ and thyrotoxic¹²⁶⁹ individuals indicate that both conditions have an abnormal epinephrine sensitiveness in common. It involves a qualitatively specific dilator response of the upper thoracic and facial skin vessels which are otherwise constricted by epinephrine. This, in turn, suggests a specific abnormality of the regional epinephrine-histamine balance^{908, 913} in both the menopausal syndrome and thyrotoxicosis.

Cyanoosis of the extremities, although less common than flushing, is also not infrequently seen in the climacteric²³⁹⁷. It occurs likewise in cases of other ovarian disturbances and of pheochromocytoma (personal observation).

Cardiac Manifestations

Further symptoms of sympathetic excitability in the climacteric are *tachycardia and palpitations*^{421, 2397} which were experienced by 73.1 per cent of a large group of subjects¹⁴¹⁶.

The occurrence of *angina-like pain* and its correlation with electrocardiographic abnormalities in menopausal women have been emphasized by Scherf^{2393, 2394}. The pain is described as being located over the precordium with occasional irradiations into the left shoulder ---

--- and is also of the character of a dull, aching pain, which may extend over hours. In view of these characteristics and the often accompanying tenderness to pressure over

tensive levels were recorded in only 10 per cent of one series of 1000 menopausal women¹⁴¹⁶, but in another statistical study the average systolic blood pressure of women of the climacteric age was found to be 144.2 mm Hg, as compared with 127.2 mm in non-menopausal women¹²⁹⁹. In the majority of cases the diastolic pressure is less elevated in menopausal hypertension than the systolic pressure^{621, 2592}. It is a matter of general experience that in many cases of menopausal hypertension the blood pressure returns to a permanently normal or near-normal level within a few years or months, even without specific treatment. On the other hand, if lability of the pressure gives way to stabilization on a high level during the climacteric period, the outlook for final normalization must be regarded as less promising. The following average figures have been given for the systolic blood pressure of women at the ages of 40, 50, and 60 years respectively: 133, 152 and 139 mm Hg¹⁷².

Therapeutic results, obtained by the application of estrogenic hormones (p 191), and the vasodilator properties of these hormones (p. 55), are believed by many observers to constitute a forceful argument in favor of the hormonal origin of menopausal hypertension. It should be emphasized, however, that it is not simply the absence of a directly vasodilating factor which seems to account for the elevation of the blood pressure but a more complex combination of active pressor mechanisms involving the adrenal cortex in its interplay with adrenosympathetic neurohormonal pressor effects (p 23 ff.).

The sympathetic tone of those women who develop menopausal symptoms appears to be generally increased, as evidenced also by other vasomotor and cardiac signs. It can be assumed to play a decisive part in the hypertensive tendency of the climacteric age. The pressor effect of epinephrine has been claimed to be increased during the menopause^{1877, 2512} which would corroborate such a view.

Artificially induced cessation of ovarian activity by x-ray treatment or castration was said to produce more marked pressor reactions than the natural menopause²⁵¹², but this was denied by others²⁵⁰³.

Occasionally hypertension may develop in the presence of an arrhenoblastoma of the ovary²⁵⁹⁷. As a rule, however, these virilizing tumors differ from the adrenogenital cortical syndrome (p 91) by not including those cardiovascular and metabolic phenomena which are due to an excess of adrenal mineralocorticoids and glucocorticoids rather than to androgens.

Flushing, Acrocyanosis

The most common and the popularly best known vasomotor manifestation of the menopausal syndrome is the phenomenon of "*flushing*". It con-

sists of a suddenly arising subjective sensation of heat ascending to the face and arms and is often followed by a cold sweat. It is accompanied by a transient reddening of the upper part of the chest, neck, and face, due to dilatation of the cutaneous vessels.

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... the shoulder and arm, but it differs significantly from genuine angina on effort in that it is not provoked in the typical fashion by physical exertion and acute emotions. It is also of a much longer duration, which may extend over hours. In view of these characteristics and the often accompanying tenderness to pressure over

the left sternal edge and fourth rib, one must agree with Scherf's interpretation of the symptom as being probably of arthralgic origin. This would coincide with the common appearance of more or less transitory arthritic changes during the climacteric¹²³⁶, for which adrenocortical factors are believed to be responsible. Nevertheless, the electrocardiogram of such cases may display the criteria of myocardial hypoxia: downward displacement of the S-T segment and flattened or inverted T^{2992, 2994} so that an increased activity of the hypoxia-producing adrenergic neurohormones can be assumed to affect the heart muscle, like other sympathetically innervated structures of the hypo-ovarian woman.

An enlargement of the heart does not occur in the menopause²⁹⁹⁷ unless some kind of hypertrophy-producing heart disease supervenes or had been in existence previously. In such cases the hormonal alterations of the menopausal state may constitute an additional threat of decompensation^{2208, 2268}, although some cardiac women pass through the critical years unharmed¹³⁴⁹.

The occasional appearance of *edema of the ankles* which may be accompanied also by facial edema and swelling of the hands^{627, 2937} is not to be mistaken for a sign of cardiac failure as long as no other definite criteria for the latter can be detected such as congestion of the lungs and liver and increased venous pressure. The menopausal edema may be related to the water retention and edema formation which frequently occur in connection with menstruation^{91, 2385, 3132, 3773, 3405} and which Thorn and co-workers^{3401, 3403} have interpreted as the result of estrogen action upon sodium and water metabolism.

Moderate *shortness of breath* on physical exertion¹⁴¹⁸ should not be overestimated as necessarily indicating cardiac decompensation, but outright attacks of nocturnal orthopnea and pulmonary edema must be regarded as serious signs. They require the customary therapeutic procedures, beside hormone treatment, even though the latter alone may suffice in an occasional case to normalize the situation²⁹⁹⁴ (p. 191).

The term "*sighing respiration*" designates the urge to take exceptionally deep breaths at relatively short intervals, sometimes even at every other respiratory period¹⁰⁹⁹, yet with a feeling of inability to fill the lungs with air to capacity. It is not specific for the menopausal syndrome and occurs also during pubescence in both sexes²⁹⁹⁷ (personal observation), in "neuro-circulatory asthenia" (80 per cent of the cases)^{122, 520, 3602} and in hyperthyroidism^{2987, 3602}, but it is far more frequently observed in women than in men²⁹⁸⁷ and especially during the climacteric^{2981, 2997}. Although it may be aggravated by assuming the recumbent position²⁹⁹⁷, it must not be confused with the orthopnea of congestive cardiac failure or with any kind of heart disease³⁶⁰². Its disappearance under treatment with estrogens²⁹⁹⁴ betrays its hormonal origin, the exact nature of which is not yet understood, however.

Treatment of the Menopausal Syndrome

In this discussion, we shall not consider those details of hormonal treatment which are directed against complications within the sexual sphere itself, but will confine ourselves to a consideration of therapeutic measures intended to alleviate the cardiovascular symptoms of the menopausal syndrome.

The administration of *estrogenic hormones* during the climacteric has been practiced ever since such preparations became available. Some older unfavorable reports were obviously due largely to the use of inadequate preparations and insufficient dosage. In general, it can be said that present-day medication with either natural estrogens or *synthetic diethylstilbestrol* yields satisfactory results in the great majority of cases, as far as flushing, paresthesias, nervousness, sweating, headaches, etc., are concerned. A critical "blind" study of the comparative efficiency of different forms of treatment¹²⁶ showed satisfactory relief, obtained by both diethylstilbestrol (0.25 mg three times daily) and the same combined with 5 mg methyltestosterone (three times a day) in 96.9 per cent and 89.6 per cent of the cases respectively. Methyltestosterone alone was about equally effective in only one-fourth of the cases, placebos were reported to give relief in 7 per cent. While nausea occurred in almost one-third of the women receiving plain diethylstilbestrol medication, it was limited to only 4 per cent under combination therapy, but, on the other hand, the addition of the male hormone produced mild acne, hoarseness and facial hair growth in 13 per cent. In another series¹²⁷, the percentage of favorable results was smaller. As the hormone treatment must often be continued over many months or even years, it is sometimes necessary, because of the side effects, to replace the oral diethylstilbestrol medication (0.5 to 1.0 mg per day) by parenteral administration of more expensive estrogenic hormones in relatively large doses, e.g., estradiol dipropionate, 2.5 mg intramuscularly twice a week for one month and repetition whenever needed. Patients with the lowest spontaneous urinary follicular hormone excretion are said to respond particularly well to this treatment.

A-ray irradiation of the pituitary gland is capable of producing favorable results.¹²⁸ However, they were found to be only transient and accompanied

by loss of temporal hair¹¹¹⁹. In an occasional case of menopausal hypertension, x-ray irradiation of the adrenals may, likewise, prove useful (Fig. 21). *Psychotherapy* is almost always indicated, especially in the case of artificial castration²⁷³⁷, and *barbiturates* help to keep the neurogenic factors of the syndrome under control.

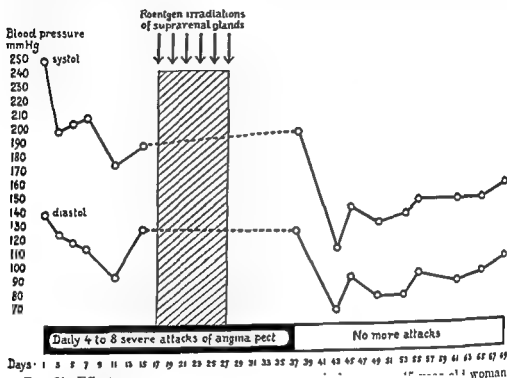


FIG 21 Effect with menopausal

The Male Climacteric; Castration

Although it is true that a combination of symptoms like that of the typical menopausal syndrome occurs only comparatively rarely in males, it does not appear justified to deny altogether its existence in men and its pathogenic analogy to the feminine syndrome. The decline of male sexual function is usually a gradual and slow one and may extend into advanced senescence, as concluded from the urinary excretion of androgens (17-ketosteroids)^{755, 1039, 1089, 1801, 1828}. The latter cannot be derived from the adrenal cortex alone, as they diminish rapidly after removal of the testes (lit., see 1845). The rise of urinary gonadotrophin excretion is also not as conspicuous in aging men as in menopausal women^{1450, 2914}. Nevertheless, the appearance of hot flashes, excessive perspiration, tachycardia, palpitations, etc.^{745, 1529, 3366}, in men between 45 and 55 years is not quite uncommon. It has been observed in about one-half of a series of patients with prostatic hypertrophy¹⁵²⁹. A somewhat increased pulse pressure was recorded in a group

of elderly men from which hypertensive cases had been deliberately excluded¹⁵⁵. This finding would suggest increased epinephrine activity.

Angina-like symptoms very much resembling those in hypo-ovarian women (p. 189), unrelated to effort, prolonged, not responding to nitroglycerine and hence probably not of cardiac origin, with or without accompanying electrocardiographic abnormalities, were seen to disappear rapidly under treatment with testosterone which also normalized the ECG¹⁵⁷.

In castrated males, a high excretion of gonadotrophins may be paralleled by neurovegetative phenomena of the menopausal type. They respond satisfactorily to treatment with testosterone propionate¹⁵⁸ (25 mg twice or thrice a week or implantation of about 300–400 mg in the form of pellets twice a year).

By comparison with the conditions arising under the influence of the climacteric or castration, the age of pubescence is relatively free from cardiovascular disturbances. Yet there are occasional instances of palpitations, sighing respiration, paresthesias, and vertigo in adolescent girls and boys¹⁵⁷ (personal observation) which are remotely reminiscent of certain features of the menopausal syndrome. A delayed or incomplete sexual development is not infrequently accompanied by the persistence of a marked juvenile type of respiratory cardiac arrhythmia into adult life¹⁶¹.

Morphological Cardiovascular Lesions and Gonads

There is some experimental evidence of an aggravation of cholesterol atheromatosis following removal of the gonads (p. 56 ff.), but it does not seem to have been statistically ascertained as to what extent the physiological decline or cessation of sexual function contributes to the progress of arteriosclerosis with advancing age. Certain observations concerning the serum lipid distribution under the influence of estrogens in menopausal women seem to suggest a possible causative role of the ovarian hormones in the lower incidence of arteriosclerosis before the climacteric¹⁶². The occurrence of coronary sclerosis is almost five times greater in men than in women¹⁶³. This was interpreted as indicating a protective effect of the estrogenic hormones¹⁶⁴, but the greater thinness of the coronary arterial walls in females from birth on⁷⁶¹ may also be considered as a factor in the sex distribution of coronary lesions. The increase in size of the adrenals after castration^{123, 166, 167, 168, 169} and in old age^{762, 2129} is compatible with the assumption that sexual involution contributes indirectly to the formation of arteriosclerosis by means of cortical hyperfunction.

Heuristic Aspects of Cardiovascular Manifestations Connected with Gonadal Hypofunction

The heuristic value of the menopausal syndrome as a source of information regarding hormonal influences upon the cardiovascular system is limited.

ited by the complexity of the endocrine interplay, but at least one negative conclusion can be drawn, especially from the sequelae of artificial castration, namely that a lack of the sexual hormones *per se* seems to be of only minor if any significance for the pathogenesis of arterial hypertension, cardiac hypertrophy and failure and genuine angina pectoris. Whatever tendency toward the development of such forms of cardiovascular pathology may be attributable to the menopausal state, must be considered from the point of view of a probable secondary participation of other endocrine organs, particularly of the pituitary and the adrenal cortex. Available pathologic and hormone-chemical data are yet too scarce to warrant any further speculations in this respect.

The characteristic phenomenon of flushing seems to be amenable to a more specific interpretation in view of (a) the fact that it can be elicited by epinephrine and (b) that it is paralleled by the flushed skin of thyrotoxic individuals. Tachycardia, palpitations and sweating are related sympathogenic features, which both conditions have in common. The paradoxical flushing effect in response to epinephrine, which normally causes pallor, occurs only in individuals with either hypogonadism or thyrotoxicosis. This suggests some peculiarities of these two states which may engender an abnormal liberation of histamine by epinephrine. The histamine-discharging⁹⁰⁹ and dual vasoconstrictor-vasodilator²¹⁰⁶ property of sympathetic ganglia and fibers suggests a delicate balance between epinephrine and histamine actions on the vascular system⁷⁰⁹. The vasodilator effect of the gonadal steroids themselves (p 54 ff) can hardly account for the phenomenon of flushing, since the latter appears in connection with the diminution or disappearance of these steroids

Summary

Certain neurovegetative cardiovascular features of the menopausal syndrome which are also occasionally seen in the spontaneous male climacteric and in castrates of both sexes, namely flushing, tachycardia, and palpitations, are probably due to an increase of sympathetic neurohormonal effectiveness (sensitization of effector cells?), possibly in conjunction with a derangement of the interplay between epinephrine and histamine. A moderately pronounced tendency toward labile or sometimes stabilized hypertension with a usually large pulse pressure, occasional edema formation and aggravation of existing heart disease, is to be attributed to secondary pituitary adrenocortical over-activity. Treatment with gonadal hormones is as a rule successful, except for hypertension.

Pregnancy (Normal and Toxemic)

The physiological state of pregnancy constitutes a spontaneously reversible shift in endocrine balance which, although not yet analyzed in all its

details, presents nevertheless an opportunity to evaluate the relationship between some of the known hormonal alterations and cardiovascular changes.

Endocrine Physio-Pathology

After implantation of the ovum in the uterine mucosa, a rapid and intense increase of gonadotrophin secretion takes place which reaches its peak during the 8th to 11th week and then declines again to near-normal values around the beginning of the 4th lunar month. This temporary increase of pituitary activity is accompanied by an enlargement of the gland and may elicit acromegaly-like symptoms as a side effect. Urinary assays indicate an about normal excretion of estrogens and of pregnanediol, the excretory form of progesterone, during the first trimester. This is followed by a gradual but marked increase of estrogen and pregnanediol excretion which continues until parturition. Many investigators suspect the placenta as its source. The chorio-placental system seems to take over the functions of both the pituitary and the ovary while the latter enters into a temporary state of inactivity. During the gestational period, the adrenals enlarge somewhat in size^{182, 207} and show an increased lipid content of the cortex. These morphological changes are accompanied by a marked rise of the urinary glucocorticoids which occurs in a double peaked curve. The first peak coincides with that of the pituitary gonadotrophins. The second maximum which equals the amount excreted between the 200th and 240th day shows a sharp decline toward term²⁰² (Fig. 202) and the excretion of total corticoids in the last trimester is about 100 mg.

As yet, the pattern of corticoid excretion during pregnancy is not clear.

The first trimester is the one during which a maximum amount of steroids (corticoids, estrogens and progestins) is present in the maternal body, while the last weeks of pregnancy are characterized by a decline of steroid-producing activity.

Other endocrine organs are also involved in the changes during pregnancy, though apparently to a much lesser and functionally not very significant extent, as indicated by an enlargement of the thyroid^{241, 252, 264} and the parathyroids²⁵³.

It is not yet definitely known in which proportion the fetal hormonal production participates in the over-all hormonal set-up of the two last trimesters, but there are various indications that the fetal cortex, which grows rapidly during the third trimester of prenatal life and degenerates again previous to birth, contributes a substantial share²⁶². The corticoid

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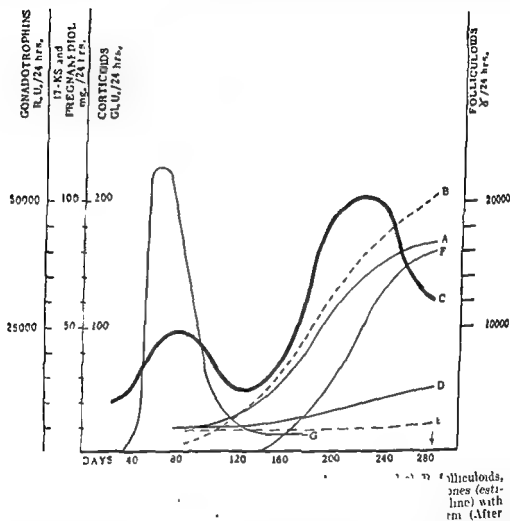
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is due to the fact that the 8th lunar month is the one during which a maximum amount of steroids (corticoids, estrogens and progesterone) is present in the maternal body, while the last weeks of pregnancy are characterized by a decline of steroid-producing activity.

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excretion of women bearing twins is greater than that of those with a single fetus³⁴⁴. The production and excretion of chorionic gonadotrophins reaches its height between the 50th and 100th day³⁴⁵. Altogether, it can be said that during pregnancy the maternal cardiovascular system is exposed to a



radically new endocrine situation, not only regarding the quantity but also regarding the origin of the hormones involved. Some of these are now furnished by both placenta and fetus in addition to the regular sources of extra-gestational life

The morphological and functional endocrine alterations which produce the so-called "toxemias" of pregnancy and especially their often fatal culminating syndrome, eclampsia, during the last months of pregnancy, are not yet clearly understood. Many theories have been advanced for their

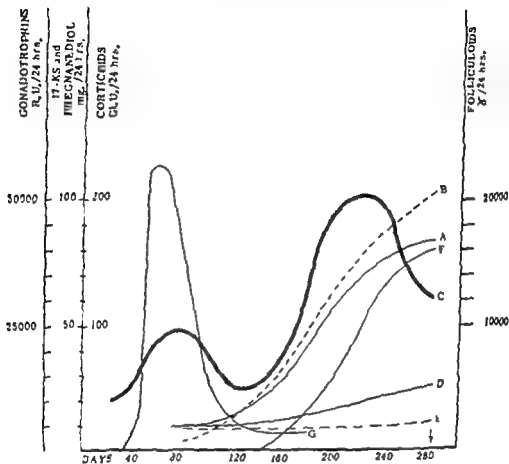
explanation, but none can be considered as definitely proven. Some investigators¹¹⁶¹ believe that a sudden, rapid destruction of estrogens, paralleled by an elevation of chorionic gonadotrophins, gives rise to an accumulation of hypothetical toxic steroid derivatives. Others suspect an excessive activity of the posterior lobe of the pituitary and of its anti-diuretic hormone^{116, 145, 146}, but it is not even known with certainty whether or not posterior pituitary substances enter into the circulation in the last stages of pregnancy, although such claims have been made in view of antidiuretic properties of the serum of eclamptic women^{116, 146}. The observation of normal delivery occurring at term in hypophysectomized animals^{1127, 1032, 1173} and the appearance of pre-eclamptic signs in pregnant women with diabetes insipidus¹¹³ do not seem to support the concept of a significant interference on the part of circulating hormones of the posterior pituitary. The finding of abnormally small adrenals in women who had died of eclampsia¹⁰⁹ was considered as an analogy to the adrenal atrophy produced by excessive administration of DCA via inhibition of the pituitary^{1250, 1209, 1034}. Accordingly it was taken as an indirect indication of preceding excessive corticoid secretion. The urinary excretion of significantly augmented quantities of total corticoids by pre-eclamptic women^{1064, 1411} points in the same direction. Surprisingly, neither the eosinophil count nor the epinephrine-induced eosinopenia were found to differ significantly in pre-eclamptic women from those observed in normal pregnancy¹⁰⁶. Since the mineralocorticoids do not affect the circulating eosinophils, these findings do not rule out a possible excessive production of this latter type of corticoids in toxemia. The placentas and urine of women with toxemia of pregnancy were found to contain large amounts of an anti-diuretic substance, not identical with the posterior pituitary hormone¹³⁴².

Hemodynamics and General Metabolism

The extensive studies by Hamilton and co-workers¹⁴¹⁰ have established certain typical features of the hemodynamics of pregnancy and the puerperium which, together with the observations of others, give a rather complete picture of the circulatory system of the pregnant woman. Although most of this work was carried out at a time when only little was known concerning the role of the hormones in hemodynamics, electrolyte and water metabolism, it is none-the-less of outstanding value for correlation with present-day endocrine concepts.

Perhaps the most conspicuous single dynamic alteration which occurs during pregnancy is the regular increase of the total circulatory volume which continues through the 9th lunar month, reaches an average 45 per cent above the normal plasma volume, and then declines toward the end of pregnancy and beyond delivery^{465, 740, 1058, 1752} until normalization occurs in

excretion of women bearing twins is greater than that of those with a single fetus³⁴⁴. The production and excretion of chorionic gonadotrophins reaches its height between the 50th and 100th day³⁶⁴⁹. Altogether, it can be said that during pregnancy the maternal cardiovascular system is exposed to a



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of the increased adrenosympathetic activity, for which there is ample evidence in the above-described cardiovascular manifestations.

Other neurovegetative signs during pregnancy are fainting spells, dizziness, sighing respiration¹²², flushing of the skin¹²³ and dilatation of the cutaneous capillary loop¹²⁴. Labor increases the blood pressure and cardiac work temporarily, but does not seem to produce any extraordinary cardiovascular phenomena^{122 125 126}.

Cardiac Manifestations (Physiological)

The electrocardiogram of uncomplicated cases shows usually a left axis deviation^{127 128 129 130 131} which progresses during the first two trimesters but may revert partially toward normal in the last weeks before delivery¹³². It is frequently accompanied by an inversion of T₂¹²⁷ and is attributed to a gradual change of position of the heart in relation to the bony chest and diaphragm¹²⁹. There is also often a deep Q in lead III^{131 132 133}. Whether or not the heart undergoes an actual enlargement during the gestational period is still a controversial question and difficult to decide clinically, because the change of diaphragmatic position is undoubtedly responsible for much of the increase in size of the radiographic heart silhouette¹³⁴. Special volumetric measurements of the heart shadow^{135 136} and the appearance of an indentation of the anterior wall of the esophagus¹³⁷ are suggestive of a real increase of heart size, possibly due to the augmented blood volume and to corticoid and/or growth hormone action upon the heart muscle. Even though animal observations did not reveal any increase in the weight of the heart during pregnancy^{138 139}, there are some indications from autopsy findings^{140 141 142} that such is the case in humans.

Soft systolic murmurs^{143 144 145} and an accentuated second sound over the pulmonary artery^{146 147} are heard in a high percentage of pregnant women. Extrasystoles occur in one-third to one-half of the cases^{148 149}. Paroxysmal tachycardia is rare¹⁵⁰.

Respiration

The vital capacity of the lungs is usually slightly increased¹⁵¹ because of greater motility of the thoracic cage¹⁵². In spite of this, there is frequently (in about 60 per cent of the cases) a certain degree of chest

Non-Cardiac Edema

Edema of the legs develops in about one out of four cases of pregnancy¹⁵³, particularly in the third trimester, infrequently at earlier stages. Neither this nor occasionally developing generalized edema needs to be interpreted

the second week post-partum. It is connected with hydration of the blood, and the coincidence of its maximum with that of corticoid production suggests renal water retention through hormonal interference^{399, 401} as its cause.

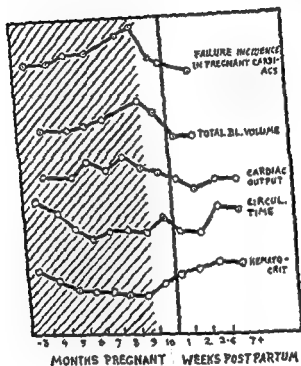
The *cardiac output* is likewise increased 40-50 per cent throughout pregnancy with the maximum in the 8th or 9th month, followed by a descent toward term and normalization a few weeks later^{448, 543, 1101, 1319, 1410, 2013, 2223}

This phenomenon has been ascribed in part to the augmented circulatory volume which is apt in itself to stimulate cardiac output⁴¹. Diminished *blood viscosity* with a minimum in the 9th month and subsequent rise toward normal may be another factor⁵⁵⁵. The individual *stroke volume*¹³¹⁹, the *heart rate*^{448, 1319} and the *velocity of blood flow*^{555, 2195} are increased. These changes are particularly accentuated during physical exercise³⁰¹⁴. Since the increase of cardiac output is considerably greater, as a rule, than the slight to moderate increase of oxygen consumption, the arterio-venous oxygen difference in the arm has been found diminished⁴⁴⁵.

While the *systolic blood pressure* does not undergo any major change in primarily uncomplicated cases of pregnancy^{55, 1037, 2159}, the *diastolic pressure* tends to be lowered^{35, 555, 590, 1484} with a resulting increase of pulse pressure^{134, 1464, 2144} which disappears again during the last month before term⁵⁵⁵. These hemodynamic alterations were interpreted by Burwell⁴⁴ as being due to the vascular structure of the placenta which would act like an arterio-venous fistula. Although this interesting theory would be well compatible with some of the hemodynamic features of pregnancy, it seems to be contradicted by the fact that the hemodynamic changes revert to normal or near-normal during the very phase in which one should expect the placenta to affect general circulation most distinctly, namely during the last weeks of pregnancy.

The possible assumption of a state of hyperthyroidism is not borne out by known facts. With only one exceptional dissenting opinion³⁰⁶³, it is unanimously agreed that despite the enlargement of the thyroid gland during gestation, the typical thyrotoxic syndrome is neither provoked by pregnancy^{541, 1107, 1319, 1620, 2405} nor an existing thyrotoxicosis aggravated. In one group of 937 pregnancies, there was no case of hyperthyroidism³⁶⁹⁴ and in another series of 50,000 pregnant women, only 28 were afflicted with it¹³¹⁹. In two series of 3678¹³¹⁹ and 7228²⁴⁰⁵ cases of hyperthyroidism, the incidence of pregnancy amounted to not more than 0.41 per cent and 0.6 per cent respectively. An elevation of the *basal metabolic rate* of 15-30 per cent, which sets in after the 12th week of gestation and attains its maximum at term, occurs as a rule^{541, 1319}, but this is generally attributed to the oxygen consumption by the added protoplasmic mass of uterine and fetal tissue^{1319, 2929} rather than to increased thyroid function. There still remains the possibility that part of the hypermetabolism is caused by calorigenic effects

With diminution of
nth, the incidence of



Labor itself is said to be tolerated comparatively well and rarely to bring on the first decompensation of a patient who had never been in failure before.¹²¹⁹ Probably the hormonal situation is more favorable by that time, compared with the preceding gestational period, and the extra hormone discharges which are connected with labor do not often transgress the critical threshold. Interestingly, the widespread belief that Caesarean section serves as a safe procedure to spare a cardiac mother the stress of spontaneous delivery seems to be erroneous, as suggested by an unexpectedly high death rate observed as a result of this major surgical intervention.^{1219, 1312.}

as a sign of congestive cardiac failure unless there are other positive indications which would prove the existence of cardiac complications. As a rule, the edema of pregnancy is not accompanied by an increase of venous pressure in the arm¹³⁴⁹. After ruling out other known causes of edema, including cardiac failure, Dexter and Weiss³²⁷ came to the conclusion in 1941 that the edema of pregnancy seems to be due to a "primary humoral etiology". Since then, various observations have accumulated which make it more than probable that this type of edema is caused by an excessive activity of sodium- and water-retaining corticoids³⁴¹¹.

Congestive Heart Failure

Although there is little evidence that pregnancy per se would form the sole etiologic factor of congestive failure in women with otherwise intact hearts, except in some cases of "toxemia of pregnancy" (p. 202), there cannot be any doubt that "cardiac" women and those with pre-existing severe essential hypertension and large hearts are facing a real danger by becoming pregnant^{1349, 1475, 2763}.

Twenty per cent of 655 cardiac women with various forms of heart disease who had never been in failure before became decompensated for the first time during pregnancy, which proved to be a much greater incidence than that seen in a similar group of non-pregnant cardiacs over a corresponding period of time¹³⁴⁹. Twenty-four per cent of maternal deaths during pregnancy were caused by cardiac complications, according to one statistical survey³³⁰². The onset of congestive cardiac failure during pregnancy occurs usually (in about 80 per cent¹²¹³) between the 24th and 36th week^{1349, 1658} with a subsequent decline during the tenth month³³⁸ (Fig. 23). Hence, the peak of the incidence of severe cardiac complications coincides with that phase of pregnancy which is characterized by the maximum of circulatory volume, cardiac output and pulse pressure (Fig. 23). It also coincides with the maximum accumulation of corticoids (maternal plus fetal) in the cardiovascular system of the pregnant woman (Fig. 22, p. 196).

In keeping with the traditional mechanistic ideology and terminology concerning cardiac disorders, the occurrence of heart failure during pregnancy is usually attributed to the circulatory "burden" or "load" in this critical phase. This terminology can no longer be accepted, unless it is with the understanding that it designates not only the mechanical "load" of an increased circulatory volume, but more essentially the chemical "load" of an excess influx into the myocardial cells of hormones which are known to upset their metabolism and electrolyte pattern. The time coincidence of maximal corticoid accumulation and of the maximal tendency to develop congestive failure in pregnant cardiacs constitutes a suggestive example of endocrine cause and cardiac effect.

believed that the retention of excessive quantities of water, both intracellularly and extracellularly, constitutes the most significant single factor accounting for the specific manifestations of eclampsia, especially by giving rise to edema of the brain²². As to the mechanism by which excessive water retention takes place, it has already been mentioned (p. 200) that it appears more likely to be caused by an abnormal pattern of secretion of sodium- and water-retaining steroids of chorionic-placental and fetal origin than to posterior pituitary interference for which no positive evidence could be detected^{22,24}. The derivation of part of the steroids, which are supposedly involved in the syndrome, from sources other than the maternal adrenal glands is suggested by the fact that both normal pregnancy^{23,25} and toxemia of pregnancy²⁶ can occur in the presence of Addison's disease. Normal conditions are rapidly restored in toxemic women after removal of the fetus and placenta from the maternal organism. The complete or almost complete absence of circulating eosinophils in eclampsia²⁴ although not a constant phenomenon²⁷ supplies a further criterion of the corticoid-like nature of the hormones which produce the so-called "toxemia". The total corticoid excretion by toxemic women in the third trimester was found almost twice as high as that of normal pregnant women^{26, 34,35}. The urine of such patients contains abnormal amounts of a "desoxycorticosterone-like" sodium retaining substance³⁶. Estrogens and progesterone may also be involved in the sodium retention leading to toxemic symptoms, but probably to a lesser extent than the corticoids. They are believed to "condition" the maternal organism for the more vigorous onslaught on the part of the corticoid hormones^{35,37}. Water storage in the lower extremities due to increased local venous pressure and leakage into the tissues may be an additional factor contributing to hydration³⁸. Pregnanediol was reported to be slightly diminished and chorionic gonadotrophin to be greatly increased in cases of severe toxemia^{39,40}.

Despite a distinct tendency toward attacks of acute dyspnea with râles and pulmonary edema⁴¹, the signs of generalized and persistent congestive heart failure are only rarely detectable in pre-eclamptic and eclamptic patients, unless the situation is complicated by pre-existing heart disease which greatly promotes the development of congestive cardiac failure in toxemic women⁴². The circulatory volume does not seem to be significantly greater in the toxemic state than in normal pregnancy^{43,44} so that purely hemodynamic factors cannot be made responsible for its grave implications.

Only a few data are available concerning the ECG in eclampsia. While some observers were impressed by a lack of abnormalities⁴⁵, marked alterations of the T-wave and one incidence of auriculo-ventricular block were described in another series⁴⁶.

Post-mortem examination of the hearts of patients who had died of

^{1654, 2302}. A large proportion of post-partum deaths occurs within the first 24 hours, which indicates a fatal role of the shock mechanisms involved.

One of the earliest signs of developing congestive cardiac failure is a decrease of vital capacity. Auricular fibrillation, which practically never occurs in non-cardiac pregnant women, is an event which forecasts grave potentialities¹⁶⁵⁴.

The management of cardiac failure in pregnancy does not differ essentially from that used in non-pregnant cardiac persons. Apart from rest, digitalis, aminophyllin, diuretics, and oxygen, a drastic restriction of sodium in the diet is directly aimed at the ammunition by means of which the corticoids seem to exert their injurious effects upon the cardiovascular system, and contributes substantially to the success of treatment^{2304, 2304}.

If interruption of pregnancy is at all contemplated, it should be carried out before the end of the third lunar month²³⁰⁴ when the hormonal burden on the heart has not yet gone to extremes. A late interruption after the eighth lunar month for purely cardiac reasons is usually not justified, as the hormonal and circulatory situation is likely to improve spontaneously during the last month of pregnancy and as the hormonal reactions to the stress of surgical intervention may be greater than those occurring in connection with delivery. With modern therapeutic techniques it is even possible to carry cardiac women through multiple pregnancies^{592, 2387}.

Toxemias of Pregnancy

Aside from the phenomenon of "pernicious vomiting" in the earlier stages of pregnancy, for which hormonal disturbances (excessive formation of gonadotrophins³⁰²², allergy to progesterone³⁰⁰) have been tentatively made responsible, the term "toxemia of pregnancy" refers to a characteristic syndrome of later pregnancy. It was found to occur in milder or severe form as "pre-eclampsia" or "eclampsia" in about 10 per cent of a large series of pregnancies in the United States¹³⁴⁹, while it is much less common among primitive peoples⁷⁴³. Its outstanding clinical manifestations consist of albuminuria, a not extreme but fixed diastolic and systolic hypertension, oliguria, marked edema, headaches, blurring of vision, epigastric pain, vomiting, convulsions, coma, and eventually death (lit., see⁷⁴⁴).

The syndrome of pre-eclampsia, that is the clinical status preceding the convulsive stage, shares various features with "essential" as well as "malignant" hypertension. Women with pre-existing essential hypertension are more likely to develop the toxemia syndrome than originally normotensive ones¹⁶⁵³. An important criterion of pre-eclampsia is the greatly delayed excretion of ingested water^{1613, 2392} which is much more marked than in patients with essential hypertension, although there is some overlapping between the milder forms of pre-eclampsia and essential hypertension⁷⁴⁵. It is

believed that the retention of excessive quantities of water, both intracellularly and extracellularly, constitutes the most significant single factor accounting for the specific manifestations of eclampsia, especially by giving rise to edema of the brain⁷⁵. As to the mechanism by which excessive water retention takes place, it has already been mentioned (p. 200) that it appears more likely to be caused by an abnormal pattern of secretion of sodium- and water-retaining steroids of chorionic-placental and fetal origin than to posterior pituitary interference for which no positive evidence could be detected^{77,78}. The derivation of part of the steroids, which are supposedly involved in the syndrome, from sources other than the maternal adrenal glands is suggested by the fact that both normal pregnancy^{77,78} and toxemia of pregnancy⁷⁹ can occur in the presence of Addison's disease. Normal conditions are rapidly restored in toxemic women after removal of the fetus and placenta from the maternal organism. The complete or almost complete absence of circulating eosinophils in eclampsia⁸⁰ although not a constant phenomenon⁸¹ supplies a further criterion of the corticoid-like nature of the hormones which produce the so-called "toxemia". The total corticoid excretion by toxemic women in the third trimester was found almost twice as high as that of normal pregnant women^{79,82,83}. The urine of such patients contains abnormal amounts of a "desoxycorticosterone-like" sodium retaining substance⁸⁰. Estrogens and progesterone may also be involved in the sodium retention leading to toxemic symptoms, but probably to a lesser extent than the corticoids. They are believed to "condition" the maternal organism for the more vigorous onslaught on the part of the corticoid hormones⁸⁴. Water storage in the lower extremities due to increased local venous pressure and leakage into the tissues may be an additional factor contributing to hydration⁷⁶. Pregnanediol was reported to be slightly diminished and chorionic gonadotrophin to be greatly increased in cases of severe toxemia⁸⁵.

... detectable in pre-eclamptic and eclamptic patients, unless the situation is complicated by pre-existing heart disease which greatly promotes the development of congestive cardiac failure in toxemic women⁸⁶. The circulatory volume does not seem to be significantly greater in the toxemic state than in normal pregnancy^{86,87} so that purely hemodynamic factors cannot be made responsible for its grave implications.

Only a few data are available concerning the ECG in eclampsia. While some observers were impressed by a lack of abnormalities⁸⁸, marked alterations of the T-wave and one incidence of auriculo-ventricular block were described in another series⁸⁹.

Post-mortem examination of the hearts of patients who had died of

^{1659, 2303}. A large proportion of post-partum deaths occurs within the first 24 hours, which indicates a fatal role of the shock mechanisms involved.

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correlation of known facts regarding the quantitative distribution of these hormones over the gestational period, and certain typical cardiovascular changes appearing during pregnancy. The experimentally established (p. 54 ff.) relative inefficiency of the sexual steroids and of the gonadotrophic hormones regarding direct effects upon the cardiovascular system, seems to be confirmed by the cardiovascular behavior throughout pregnancy: (a) absence of significant circulatory alterations in the first trimester during maximal production of gonadotrophins, and (b) regression of certain later occurring characteristic circulatory phenomena near term, when estrogens and progestins attain their maximum. On the other hand, there exists a remarkably close time coincidence between the peak of the corticoid curve (8th and 9th lunar month) with the climax of those cardiovascular phenomena which are attributable to an excess action of salt- and water-retaining cortical steroids. These phenomena, which have much in common with the hyperadrenocortical syndrome, are the following: augmentation of total circulatory volume (chiefly plasma), edema, development of congestive cardiac failure (in patients with pre-damaged hearts) and of the toxemic syndrome with arterial hypertension, oliguria, albuminuria and severe pulmonary congestion. The formation of abdominal striae is another feature suggestive of a relationship to the hyperadrenocortical syndrome.

Cardiovascular indications of an increased sympathetic tone such as

... of a sympathetic background and the ultimate cause of this apparently exaggerated adrenergic neurosecretory activity remains an open question for

th... upon a maternal organism, suddenly deprived of its supply of fetal corticoids, while its own adrenals may have descended into a state of cortical inactivity due to the pituitary-inhibiting influence of excessive amounts of fetal corticoids before delivery. This concept seems to be supported by a subnormal eosinopenic response to epinephrine in the early puerperium²². It would suggest the advisability of a protective administration of adrenal extracts after delivery.

The role of the posterior lobe of the pituitary both in the physiology and pathology of pregnancy is still obscure and altogether so doubtful that no attempts are being made at this time to...

The progress achieved during the... especially concerning the adrenal... hormones, has invalidated certain older mechanistic views of the cardiovascular complications of pregnancy. However, it is still justified to describe pregnancy as a heavy, sometimes fatal "burden" on the cardiovascular

eclampsia did not prove very impressive: few distinct focal necrotic lesions and only moderate leukocyte infiltrations were seen, but a marked edema of the heart muscle was observed as a prominent feature^{1227, 1249, 1593, 2261}.

In the majority of cases, the cardiovascular status of toxemic, otherwise healthy women returns to normal within a short time following termination of pregnancy²²⁴³. A follow-up over longer periods disclosed a somewhat accentuated trend toward later appearance of hypertension within about seven years¹⁴¹⁹. This does not necessarily mean that the toxemia *per se* contributes to those later developments; it only suggests a constitutional disposition of such individuals which might render them particularly susceptible to cardiovascular disturbances during pregnancy. The greater incidence of the toxemia syndrome in women already afflicted with essential hypertension and the greater severity of symptoms during pregnancy in such cases point in the same direction. Sympathectomy seems to protect hypertensive women to some extent from toxemic complications in subsequent pregnancies^{1337, 1740}.

No reliable measures are yet available to forestall the onset of pre-eclampsia, but its hazards can be reduced by drastic salt restriction in the diet and by an even distribution of the daily water intake in small hourly installments of 150 to 200 cc each, which is said to be better tolerated than the irregular ingestion of larger amounts of water⁷⁴⁵. However, the total water intake must also be reduced in some instances¹³⁴⁹. The complications of severe toxemia may arise quite suddenly with only little premonitory evidence of impending trouble. Paroxysmal dyspnea is an alarming sign of serious import. It requires strictest supervision, rest, oxygen administration and digitalis medication, with the probability of an inevitable interruption of pregnancy in mind. An apparent amelioration immediately following an attack of dyspnea may be treacherous and recurrences must be expected at any time²⁷⁶¹. According to Hamilton and Thomson¹³⁴⁹, the general rule not to terminate pregnancy in the third trimester has to be disregarded in such cases.

Therapeutic attempts to correct the problematical hormonal derangement of toxemia by administration of estrogens, progesterone and pregnanediol¹³⁶¹ are only of theoretical interest so far, and should not detract from the necessity of radical measures of proven value.

Heuristic Aspects of the Cardiovascular Manifestations of Pregnancy

The rapidly increasing, though still fragmentary information regarding the hormonal patterns of the different stages of pregnancy indicates that pituitary and chorionic gonadotrophins, estrogens, progestins and corticoids of maternal and fetal origin are prominently involved. It suggests a close

Pancreas

Diabetes Mellitus

Extensive experimental and clinical evidence makes it certain that a deficiency of insulin is fundamentally involved in the pathogenesis of diabetes mellitus. However, it appears more than questionable that this deficiency is under all circumstances a primary and absolute one. On the contrary, there is good reason to believe that in many instances of diabetes the quantitative insulin production of the pancreas does not deviate significantly from normal and that it would be quite adequate were it not for the interference of other endocrine factors, chiefly pituitary and adrenocortical in origin. The role of insulin seems to consist essentially in preventing the "diabetogenic hormone" of the pituitary from inhibiting the enzymatic action of hexokinase which promotes phosphorylation of glucose to hexomonophosphate. Hence, the endocrine situation and its implications concerning the cardiovascular system must be considered not only in terms of a primary deficiency of insulin production but perhaps even more so in terms of alterations of pituitary and adrenocortical functions, even though the latter are only poorly understood as yet.

Endocrine Pathology

Degenerative changes of the pancreatic islets were first described in diabetics by Weichselbaum in 1901²⁵². They furnish the visible proof of a derangement in the internal secretory activity of the pancreas but they are by no means a constant finding in all cases of diabetes. Especially in diabetics of the younger group, this phenomenon is only infrequently encountered, while it is more regularly seen in persons older than 40 years and particularly in those whose diabetic condition had existed for more than 10 years²⁵³.

Despite the absence of constant significant alterations in the perceptible morphological structure of the anterior pituitary²⁵⁴, there exist various experimental and clinical facts suggesting that the original disturbance which ultimately leads to diabetes is located in the anterior lobe of the pituitary rather than in the pancreas. Hydropic degeneration of the islet cells as well as diabetes were experimentally elicited in animals by the injection of crude anterior pituitary extracts^{255, 256, 257, 258}.

system, that is, an essentially chemical and electrophysical "burden" of steroids and catecholamines, acting against the metabolic and functional integrity of the cardiovascular cell. Those patients who develop congestive heart failure as a result of pregnancy may be ranged in the category of "cortico-cardiacs" with the qualification that the offending corticoids are probably prevailing of fetal origin.

Summary

Cardiovascular manifestations of early pregnancy are characterized chiefly by an augmented sympathetic tone without abnormal thyrogenic potentiation. This factor continues throughout pregnancy but during the later stages the situation becomes more complex through the interference of a markedly increased production of salt- and water-retaining corticoids, probably largely of fetal origin. Depending on the original cardiovascular status of the individual pregnant woman (normal or pre-existing heart disease, hypertension), the combined metabolic action of excess corticoids and adrenosympathogenic catecholamines upon the cardiovascular contractile cellular elements will not or will produce circulatory derangements, such as severe hypertension, acute pulmonary edema, and congestive heart failure, possibly ending in death. The syndrome of "toxemia of pregnancy" seems to be closely related to an overactivity of fetal corticoids in the third trimester.

The situation post-partum is likely to be influenced by a temporary deficiency rather than by an over-production of maternal corticoids.

Further clarification of the hormone pattern during and after pregnancy should furnish valuable criteria for the interpretation of pathogenic factors operating in the origin also of various related cardiovascular disorders not connected with pregnancy.

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Despite the absence of constant significant alterations in the perceptible morphological structure of the anterior pituitary²⁵⁶, there exist various experimental and clinical facts suggesting that the original disturbance which ultimately leads to diabetes is located in the anterior lobe of the pituitary rather than in the pancreas. Hydropic degeneration of the islet cells as well as diabetes were experimentally elicited in animals by the injection of crude anterior pituitary extracts^{256, 257}. In humans, frank diabetes developed as a side effect during the administration of ACTH^{258, 259} and diabetes occurs comparatively frequently (33-40 per cent) in patients with acromegaly.^{21, 215, 271, 287, 297, 300, 312} Experimental pancreatectomy-

induced diabetes responds to hypophysectomy with an alleviation or disappearance of its symptoms¹⁵⁵¹ but is aggravated if anterior lobe extracts are injected¹⁵⁵². The urine of acromegalic diabetics contains large amounts of anterior pituitary-like material which, if injected, produces insulin insensitivity in animals¹⁵⁵³.

On the other hand, a probably secondary mediating involvement of the adrenal cortex in some types of diabetes can be indirectly concluded from the general interference of cortical steroids in carbohydrate metabolism²⁰³¹, ²³³⁷, from the provocation of diabetes by cortisone medication²¹⁹⁶, from the lowered sugar tolerance or presence of full-fledged diabetes in patients with adrenal cortical hyperplasia or tumors²¹⁰⁸, ²¹¹⁶, ²¹⁸⁷, ²²¹⁸, from the improvement of experimental diabetes by adrenalectomy²⁰⁵⁴ and from the disappearance of clinical diabetes in patients with a cortical tumor after removal of the latter²¹⁸⁷. Nevertheless, it must be kept in mind that not every type of adrenal cortical hyperfunction gives rise to a striking derangement of carbohydrate metabolism, and that not even a normally functioning adrenal cortex is necessary for the development of diabetes, as exemplified by the occasional occurrence of a highly insulin-sensitive form of diabetes in patients suffering from Addison's disease, which is accompanied by degeneration of the islets⁷⁰ ¹²²⁹, ¹⁷⁹¹, ²³³⁸. Available reports on the morphologic condition of the adrenal cortex in diabetics do not disclose any clear-cut abnormalities²³⁰⁴. The eosinopenic response to surgical trauma and to subsequently injected ACTH was found somewhat diminished in 10 out of 23 diabetic patients⁹⁷⁶, suggesting a reduced cortical functional reserve in these cases.

Results obtained by biological assay of corticotrophic material in the blood showed the presence of abnormally large amounts of such substances in diabetics with acromegaly, Cushing's syndrome and obesity, while in other types of diabetic patients an increase was only irregularly seen¹⁵⁶. The urinary excretion of both 17-ketosteroids and glucocorticoids was reported as being normal¹⁰²⁹ ²⁴⁶⁴ or slightly lowered¹⁰¹⁸, ²¹¹⁵ ²³²⁵ ²³³³ in diabetics. Sympathomimetic catecholamines were found within normal limits²⁵⁷¹ in the blood of diabetic individuals, but the not infrequent co-existence of pheochromocytomas with hyperglycemia or full-blown diabetes¹¹⁷⁷ ²⁶⁵³ suggests some involvement of sympathomimetic action in the metabolic set-up of at least these particular forms of diabetes.

Although the thyroid hormone mobilizes liver glycogen and although diabetes occurs in an occasional case of thyrotoxicosis, there seems to be little reason to attribute to the thyroid gland any major significance in the pathogenesis of ordinary diabetes, since characteristic signs of hyperthyroidism are only rarely seen in diabetic individuals. The basal metabolism does not deviate from normal, as a rule¹²²⁰

The onset of diabetic coma and of its cardiovascular features seems to be initiated in some rare cases by thyrotoxicosis²⁴⁴, menstruation^{245, 246, 247} or toxemia of pregnancy²⁴⁸.

Blood Pressure

Statistical evaluations of the incidence of arterial hypertension in diabetic patients^{249, 250, 251} confirm the old experience of a distinct hypertensive tendency among such individuals, as compared with normal persons of the same age groups^{251, 252}. In a series of 300 diabetics, systolic blood pressure levels above 140 mm Hg were encountered in 81.4 per cent of the cases²⁴⁹ and 19 per cent of 292 patients with essential hypertension were diabetics, while diabetes was present in only 7 per cent of 3390 unselected patients of one hospital²⁵³. It is of interest to note that the high incidence of hypertension does not seem to become conspicuous before the age of 35^{251, 252}. Whether this is due to a causal relationship between the actual duration of diabetes and the onset of hypertension, or to a fundamentally different endocrine situation in the younger diabetics, as suggested by Kylin²⁵⁴, cannot be decided at this time. With advancing age, the discrepancy in the average blood pressure levels of diabetic and non-diabetic individuals increases steadily^{255, 256}. No direct relationship between the degree of hypertension on the one hand and the severity of diabetes and body weight on the other was demonstrable statistically^{257, 258}. Unfortunately, most reports concerning the blood pressure of diabetics do not

... a relatively low diastolic pressure, would indicate a loss of elasticity of the great vessels due to arteriosclerosis rather than the general vasoconstriction which causes essential hypertension. In one statistical study²⁵⁹, the increase of the average systolic pressure proved more marked than that of the diastolic pressure, so that the mean pressure did not show any impressive elevation. This might be construed as pointing toward a prevalence of the arteriosclerotic type of hypertension among diabetics. Chronic pyelonephritis may act as a contributing factor, particularly in diabetic women²⁶⁰. Diabetes with hypertension, albuminuria, and nephrotic edema, the so-called "Kimmelstiel-Wilson syndrome"²⁶¹, was observed in both younger and older age categories²⁶² in 33 per cent and 16 per cent respectively of the cases. It is connected with extensive hyalinization of the renal glomeruli (p. 214).

Neither symptomatic hypertension with its characteristic nature of

... arrangement. However, it seems

significant that in cases with adenomata of the adrenal cortex, hypertension and diabetes occurred five times as frequently as in cases without such cortical changes²⁹⁰⁷.

When accumulation of ketone bodies and coma supervene in uncontrolled diabetes, the grave clinical picture, consisting of acidosis, dehydration and air hunger is often accompanied by a fall of the systolic blood pressure to levels below 90 mm Hg and by a marked reduction of the circulatory volume and venous pressure^{303, 852, 1639, 1576, 2584} which may end in death. During coma both sodium and potassium are lost in large quantities^{90, 1056, 1551, 2221, 2438} and major functional changes in the pituitary-adrenal system can be suspected as participating in the clinical developments. Yet, these secondary complications are not to be made responsible for the onset of the acidosis syndrome which is primarily caused by the excessive oxidation of fatty acids in the liver²²²¹.

Cardiac Manifestations

There are no cardiac abnormalities which could be described as being specific for the diabetic patient. However, modern therapy raised the life expectancy of diabetics of the 10-year age group by an average 38.5 years and that of the 50-year age group by an average 6.4 years. Through this remarkable prolongation of the diabetic state it has become evident that the degenerative forms of heart disease, which diabetics of preceding generations had escaped through an earlier death, occur in diabetic individuals with greater frequency than in non-diabetics of a comparable age; in other words, the diabetic state seems actually to favor the development of heart disease, especially of angina pectoris. This seems to be due essentially to a markedly enhanced occurrence of coronary sclerosis in the older age groups. The incidence of coronary disease in younger diabetics on the other hand has remained a comparative rarity¹⁴³⁵.

Since 210 cases of *angina pectoris* had been registered among 7000 diabetics in 1931 by Root and Graybiel²⁸⁴⁷, the frequency of such cases has increased to 413 among 11,000 in 1945, as a result of the diminution of other causes of death¹⁶⁹⁰. In only 4 per cent of 210 diabetic angina cases did the onset of angina precede that of diabetes and in 90 per cent of the cases an average of nine years of existing diabetes had elapsed before angina became manifest, so that a causative role of diabetes seems to be well established in this respect. The about equal occurrence of coronary disease in female and male diabetics^{1435, 2252, 3506}, as contrasted with the relation of about 1:4 in non-diabetic individuals³⁴⁴⁵, furnishes another argument in favor of a specific angina-evoking influence of diabetes, but the endocrine mechanisms involved still remain obscure.

Only few details can be found in the literature concerning the occurrence

of myocardial insufficiency and congestive heart failure in diabetic patients. An extensive statistical survey from the Medical Clinic in Zurich reveals a very high incidence of such cardiac phenomena in the hospitalized diabetic patients with a total average of 32 per cent among men and 37 per cent among women. A maximum of 52 per cent was recorded in women beyond the 60th year. Significantly, no signs of cardiac failure were found in diabetic patients younger than 40 years¹²⁵. All diabetic percentages were on an average 15 per cent higher than those calculated for the total number of cardiac patients in relation to the numbers of all patients hospitalized during corresponding time periods. Thus, the occurrence of congestive cardiac failure seems likewise to be specifically increased in adults after the age of 40 by whatever endocrine factors are responsible for the pathogenesis of diabetes and of its cardiovascular complications. A fluoroscopically discernible enlargement of the heart, however, was encountered in a considerably lower percentage than one would have expected with regard to the high incidence of hypertension¹²⁵.

Electrocardiographic changes are frequently seen in the older age group of diabetics, in keeping with the presence of coronary sclerosis and occlusion and of arterial hypertension. There are no specific features which would distinguish them from the electrocardiographic alterations attending the same types of cardiac pathology in non-diabetic individuals, except that the "left ventricular strain pattern" was conspicuously absent in an entire series of 38 hypertensive diabetics, in the majority of whom no cardiac hypertrophy was detectable¹²⁶. Whether these limited observations do or do not prove a relatively low tendency toward cardiac hypertrophy in diabetics in general cannot be decided at this time. In one series of diabetic patients with angina pectoris, 60 per cent showed abnormal electrocardiograms¹²⁷. Twenty per cent of those who displayed an inverted T in lead I died within one year. Auricular fibrillation does not seem to occur with particular frequency in diabetics¹²⁸. It is conceivable, however, that transient heart block and the Stokes-Adams syndrome are provoked to some extent by the metabolic condition prevailing in the heart muscle of diabetic patients^{129, 130, 131, 132}.

More specific electrocardiographic manifestations are

injection
ing a re-
interval,
the latter phenomenon have been amply confirmed^{133, 134, 135}. Both the
prolongation of Q-T and a reversible flattening or inversion of the T-wave,
which is likewise attributable, at least in part, to the loss of potassium,
are often aggravated during the days of recovery from coma under intensive
treatment¹³⁶. Some other factors, such as the blood calcium and magnesium

significant that in cases with adenomata of the adrenal cortex, hypertension and diabetes occurred five times as frequently as in cases without such cortical changes²⁹⁰⁷.

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calorie regime with adequate insulin dosage seemed to exert beneficial effects by way of a depression of the blood cholesterol levels²⁷². It has been claimed to prevent the premature occlusive vascular disease in the legs of diabetic individuals and to delay its onset until that age in which it would be likely to occur also in non-diabetics²¹⁸.

Cholesterol appears to serve as a precursor of adrenal corticoids²⁶¹² and the repeated implantation of adrenal cortical tissue has been seen to be followed by the development of endarteritis-like lesions in the peripheral vessels of animals^{1574 1575 2185}. One might feel tempted, therefore, to think of a possible aggravating role of alimentary cholesterol in the progress of peripheral vascular sclerosis both by increasing the formation of pathogenic corticoids and by being directly deposited in the intima of the peripheral arteries. It is too early, however, to attach any definite significance to such speculations. The increasing occurrence of diabetic gangrene with advancing years beyond the age of sexual maturation, as well as the abolition of the usual sex differences in the distribution of peripheral vascular disease between non-diabetic men and women^{158 159}, might suggest some relationship with the sexual steroids or the gonadotrophins, but here again no really tangible evidence is yet at hand.

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retinitis, and retinal hemorrhages, which may be associated with exudates¹⁴⁸⁴ of the macular region, with narrowed arteries and engorged or obliterated veins¹⁴⁸⁷, are often characteristic enough to enable the ophthalmologist to arrive at the diagnosis of diabetes from this criterion alone. Diabetic retinitis rarely makes its appearance before the age of 40.

General Arteriosclerosis

The widespread belief that arteriosclerosis in general occurs with greater frequency in the diabetic population (approximately 500,000 in the United States¹⁷¹³) requires correction insofar as it is not so much the over-all incidence of diabetic arteriosclerosis which differs from that of arteriosclerosis in non-diabetics, but rather its severity¹⁴⁸⁷, its relatively early appearance^{231 274 2361 2115 2164}, its equal incidence in both sexes¹⁷⁷ and the pattern of its distribution in the vascular tree. The degree of arteriosclerosis seems to be influenced by the duration of pre-existing diabetes rather than by its intensity¹⁵¹².

Patchy atheromatous thickenings of the intima of the large vessels, calcifying media necrosis of the Monckeberg type and

8

6

... and leg vessels^{1484 2207}

levels, acidosis, hyperventilation, complicating coronary thromboses, and the effects of therapeutically administered insulin, must also be considered in the evaluation of the ECG during and after diabetic coma. The changes induced by insulin will be discussed on p. 221.

Peripheral Vascular Disease; Gangrene

Peripheral vascular disease of the arteriosclerotic type, like coronary disease, is not a specific feature of diabetes; but it is in a specific fashion accentuated by the diabetic condition of the body³⁴⁸ or rather by the pathogenic endocrine mechanisms involved. As a rule, there is no proportion between the severity of diabetes and the occurrence of gangrene³¹², but age³¹² and tobacco smoking³⁵² seem to act as decidedly aggravating factors.

According to one statistical survey⁷⁷⁹, *arterial lesions in the legs occurred 11 times more frequently in diabetic cases than in non-diabetics, and among women, obliterating arteriosclerosis was found to be 80 times as common in diabetics as in non-diabetics.* An even higher incidence of peripheral vascular disease in diabetics was estimated by Root²⁴⁶ from a study by other investigators²⁸⁴ who, however, were unable to detect any qualitative differences between the manifestations of occlusive peripheral vascular disease in diabetic and non-diabetic patients. These changes consist of atheromatous thickening of the intima and necrosis of the media, followed by calcification which can be readily visualized on the roentgen photograph, and finally obliteration of larger arterial branches. As a rule, the simultaneous development of small collateral vessels prevents dry mummification of those tissue sections which are deprived of their original arterial blood supply, and wet gangrene, usually complicated by bacterial infection and lymphangitis, is the result. It is apt, in turn, to give rise to septicemia and thus may decide the fate of the patient. Unless vigorous antibacterial treatment is instituted in time, the danger for life is great because of the low resistance of diabetic patients to infections (lit., see ²³¹⁰).

Impending vascular difficulties are ushered in by *intermittent claudication* and nocturnal pain in toes or heels. Several tests can be applied for their early objective recognition and for the demarcation of threatened areas: palpation and radiography of the leg vessels, blanching of the leg on elevation, intradermal histamine or saline wheal tests, measurement of the skin temperature during artificial hyperthermia, diagnostic sympathetic blockage, etc. Details must be looked up in textbooks on cardiovascular or peripheral vascular diseases.

Various theories have been advanced regarding the pathogenic factors which are supposed to form the background of peripheral vascular sclerosis in general, and in the diabetic patient in particular. The cholesterol content of the diet has received special attention, since a high-carbohydrate low-

extrasystoles, auricular fibrillation, anginal pain, depression of S-T and alterations of the T-wave can be elicited in cardiacs by insulin¹⁰⁷¹. The subjective condition of the patient may be worsened, even if the blood sugar levels are not deeply depressed¹²⁰⁶, and death may be precipitated¹²⁰⁴. Decisive factors in the provocation of the above-enumerated untoward complications are in all likelihood the reactive discharges of epinephrine and stimulations of sympathetic neurosecretion (p. 50) with their myocardial hypoxia-producing effects. An abrupt depression of the blood sugar level per se may elicit an additional disturbance of cardiac metabolism¹²⁰⁸. Moreover, a sensitization of the carotid sinus reflex mechanism of diabetic patients by insulin was seen to result in cardiac standstill¹²⁰⁶ and has been mentioned as a possible cause of sudden death of insulinized diabetics during surgical procedures, involving traction and pressure on the neck.

If insulin must be given because of the severity of the diabetes, because of an intercurrent infection with temporary lowering of the sugar tolerance, or because of impending surgical intervention and the like, care has to be taken by cautious dosage and sufficient carbohydrate administration that hypoglycemic reactions be strictly avoided. Maintenance of a moderately elevated blood sugar level and a slight glycosuria are preferable to the immediate cardiac dangers of an even mild hypoglycemic episode, regardless of the fact that an optimally corrected metabolic situation would offer the benefit of better long-range protection against the insidious progress of arteriosclerotic complications¹²¹¹. In general, it is important to keep the fat and cholesterol intake low within a low-calorie but relatively high-carbohydrate diet^{1216 1220 1221} containing 125-150 grams daily. Naturally, such a regime requires the use of insulin more often than was the case with some of the older diet forms of the pre-insulin era when large quantities of fat were prescribed to the ultimate detriment of the cardiovascular system of those patients who survived long enough to develop severe arteriosclerotic lesions.

The coincidence of coronary thrombosis with diabetes creates special problems in that a coronary episode can be diagnostically mistaken for the onset of coma and made worse by over-zealous anti-coma measures. If coma is actually precipitated by coronary occlusion, the latter may remain unrecognized and untreated¹⁰⁶⁶. A particularly careful and untiring supervision of the metabolic as well as the cardiovascular developments is imperative in such cases in order to avoid insulin hypoglycemia, over-hydration, hypopotassemia, etc., on the one hand, and under-dosage of insulin on the other. The general principles of treatment for coma, as extensively described in various textbooks^{312 1090}, apply also to the specific cardiovascular features resulting from diabetic acidosis, namely reduction of circulatory volume and myocardial weakness, for which the concomitant

²³⁴⁶. The involvement of renal and cerebral arteries seems to be about equal in diabetic and non-diabetic individuals²³⁵¹. With the number of deaths from coma markedly decreasing since the advent of insulin, arteriosclerotic lesions have become more important in the clinical picture of the average diabetic, because of the higher age attained by him. Arteriosclerosis was considered as responsible for 67 per cent of all deaths of diabetics in 1947²³⁴⁶. On the other hand, improvements of the dietary management, especially the introduction of a high-carbohydrate, low-calorie diet which was made possible by the availability of insulin, seem to have exerted a retarding influence upon the progress of arteriosclerotic lesions^{2346, 2724}, possibly through depression of the blood cholesterol levels and of adrenal cortical steroid formation. Nevertheless, the mortality from coronary sclerosis and occlusion is apparently still on the increase. Its incidence among diabetics has gradually doubled during the first half of our century²³⁴⁶ and was found autoptically to comprise 52.7 per cent of diabetics who died after the 50th year, as contrasted with only 8 per cent in a large series of non-diabetic individuals²⁴¹⁹.

Hyalinization of the glomeruli of the kidney, accompanied by marked fatty degeneration of the renal arterioles, constitutes the morphological substrate of the so-called "*Kimmelstiel-Wilson syndrome*"¹⁷⁶³ (p. 209). It is not found exclusively in combination with diabetes^{1207, 1573}, but its more severe forms are almost entirely limited to diabetic patients, largely of the younger age categories^{1207, 1573, 1765, 2446}. Anatomical lesions of this type were recorded in 9 per cent to 64 per cent of autopsied cases of diabetes^{1207, 1461, 1597, 2517}. Periarteritis nodosa seems to occur in diabetics only in very exceptional instances^{2079, 2446}.

Treatment of the Cardiovascular Complications of Diabetes

The routine forms of treatment for some of the cardiovascular diseases occurring in connection with diabetes, such as hypertension, angina pectoris, cardiac failure and peripheral vascular disease, do not differ fundamentally from those applied in analogous conditions in the non-diabetic patient. However, the coexistence of the diabetic state must never be lost sight of and special measures have to be taken to keep it under control, as well as to avoid anti-diabetic over-treatment which may nullify any gain achieved by direct cardiovascular medication.

In elderly patients and in those with signs of advanced arteriosclerosis, particularly of coronary sclerosis, it is preferable, whenever the metabolic state is not satisfactorily controlled by insulin, to avoid the use of hypoglycemic drugs, since they may severely aggravate an existing angina or congestive heart failure^{2331, 2306}, or even bring unsuspected cardiac complications to the fore²⁵³¹. Tachycardia,

extrasystoles, auricular fibrillation, anginal pain, depression of S-T and alterations of the T-wave can be elicited in cardiacs by insulin²²⁴. The subjective condition of the patient may be worsened, even if the blood sugar levels are not deeply depressed²²⁶, and death may be precipitated²²⁶. Decisive factors in the provocation of the above-enumerated untoward complications are in all likelihood the reactive discharges of epinephrine and stimulations of sympathetic neurosecretion (p. 50) with their myocardial hypoxia-producing effects. An abrupt depression of the blood sugar level per se may elicit an additional disturbance of cardiac metabolism²²⁶. Moreover, a sensitization of the carotid sinus reflex mechanism of diabetic patients by insulin was seen to result in cardiac standstill²²⁶ and has been mentioned as a possible cause of sudden death of insulinized diabetics during surgical procedures, involving traction and pressure on the neck.

If insulin must be given because of the severity of the diabetes, because of an intercurrent infection with temporary lowering of the sugar tolerance, or because of impending coma, it must be given in a judicious manner, taken by hypoglycemia.

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loss of electrolytes seems to be largely responsible. Aside from insulin medication, which may have to go far beyond 1000 units within the first 24 hours, and the application of warmth, the parenteral (intravenous or, if necessary, intrasternal) infusion of repair solutions will help to correct the disturbance underlying the circulatory collapse, but an additional intravenous use of coramine^{245, 241} at intervals and of strophanthin^{245, 142a} proved also useful in improving the cardiovascular status, especially in elderly and debilitated patients. Against drip infusions of epinephrine, which have been recommended to elevate the blood pressure level^{245, 1630, 1888}, some serious objections must be raised: not only does epinephrine antagonize the metabolic action of insulin, but it also interferes with the efficiency of cardiac oxygen consumption and it acts as an over-all vasodilator (p. 6, 11 ff.) aside from heart-stimulating effect. If any sympathomimetic pressor agent is to be considered at all, the substance of choice should be nor-epinephrine. It is an over-all vasoconstrictor, its specific effects upon the heart are largely compensated by vagal counter-reflexes and its interference in carbohydrate metabolism is negligible (p. 6, 9). Although it has not yet been given a trial in diabetic coma, the writer would expect from his own experience with numerous nor-epinephrine infusions that a dosage of 0.2-0.3 micrograms/kg./min. ought to be safe and promising for the purpose of vasoconstrictive elevation of the blood pressure.

As far as the intravenous infusion of glucose in the emergency treatment of coma is concerned, certain possible adverse side effects^{1630, 2449} may make its use inadvisable in a hospital with ample laboratory facilities and with personnel to carry out frequent blood sugar determinations, intended to prevent the danger of hypoglycemia. Under average circumstances, however, an exaggerated authoritative condemnation of glucose as a means of "blind" protection against hypoglycemia is apt to frighten the treating physician into a disastrous attitude of timid insulin under-treatment to avoid the cardiovascular hazards of possible over-dosage, even though the insulin sensitivity is vastly decreased during coma.

In the case of excessive loss of potassium during diabetic acidosis, and especially in the period of recovery from coma^{205, 1056, 2231}, as manifested by electrocardiographic signs (p. 211) and by muscular weakness, gasping respiration, large pulse pressure and high venous pressure¹⁰⁵⁶, the oral administration of potassium chloride (2 grams once or repeatedly) may become necessary.

Prevention, or at least postponement of peripheral vascular disease and gangrene in diabetics can be expected from the intake of a *high-carbohydrate, low-calorie diet*^{2316, 2724}, from avoidance of tobacco smoking, of exposure to extreme temperatures, of injury, friction and local infection

of the feet^{112, 119}. Once the signs of vascular disease have become manifest, mechanical measures (Buerger's exercises, compression and decompression devices, oscillating bed, etc.) and mild temperature influences¹²¹ are of a certain limited usefulness for improvement of circulation in the legs. The local and general application of anti-bacterial agents will help to combat infection, but in many cases surgical intervention becomes sooner or later inevitable. Even with the use of insulin and antibiotics, only about 40 per cent of diabetic patients will survive longer than three years after amputation of one leg, and 40 per cent of the survivors are likely to lose the second leg¹¹¹. It may be, however, that with more extensive use of lumbar sympathectomy and new sympatholytic drugs, the prognosis of diabetic gangrene will be considerably improved¹²².

Intra-arterial injection of ether was at one time enthusiastically advocated¹²³, but does not seem to have been tried on a large scale.

Heuristic Aspects of the Cardiovascular Complications of Diabetes

The amount of firmly established information regarding the endocrine factors responsible for the pathogenesis of diabetes in general and for the individual case of diabetes in particular, is disappointingly small if measured against the sum of labor which has been devoted to their elucidation. Nevertheless, the fundamental participation of both the anterior lobe of the pituitary and of the pancreatic islets in certain experimental forms of diabetes can be assumed almost with certainty to apply likewise to the origin of human diabetes and of those cardiovascular abnormalities which are perhaps not caused but certainly aggravated by the diabetic state.

Various circumstances compete in blurring the issue: the problematical nature of the "diabetogenic hormone" of the anterior pituitary, the lack of methods for its assay and for the assay of insulin, the lack of direct evidence for a quantitative increase of adrenal corticoid function in diabetes, the undisclosed role of central nervous and neurosecretory function and of other endocrine factors, the existence of different, not too clearly distinguishable varieties of diabetes, such as the juvenile and senile types, the more or less insulin sensitive or insulin resistant forms of diabetes, etc.

As long as detailed hormone assays will not have clarified the actual endocrine patterns, which operate in diabetes mellitus --

... probably involved in the diabetic situation, is suggestive of anterior pituitary and adrenocortical influences acting upon the cardiovascular tissue elements in a detrimental fashion, but this is about all that can be said at the present time. The hypercholesterolemia of diabetes and the derangement of the intermediary

carbohydrate metabolism are likely to serve only as contributory pathogenic factors, as far as cardiovascular pathology is concerned

Summary

Only two forms of cardiovascular lesions which occur in diabetic individuals may be considered with some reserve as being specific for this disease, namely intercapillary glomerular sclerosis (Kimmelstiel-Wilson) and diabetic retinitis, insofar as analogous lesions are relatively uncommon and usually less severe in non-diabetic patients.

The development of general arteriosclerosis (calcifying intima-lipoidosis, media-sclerosis and arteriolar sclerosis) is hastened and aggravated by the diabetic state with particular predilection of the coronary and leg vessels and with abolition of the usual sex ratio in the occurrence of these latter vascular involvements. Hypertension and angina pectoris are likewise accentuated in the diabetic population, but cardiac hypertrophy does not seem to appear more prominently among diabetics than among non-diabetics.

The cardiovascular manifestations of diabetic coma are largely determined by dehydration and loss of electrolytes and have to be treated accordingly.

The still prevailing uncertainty, concerning the nature and distribution of hormonal (chiefly pituitary, adrenocortical and pancreatic) influences responsible for the diabetic state, precludes also a clear interpretation of the factors which cause the above-named cardiovascular peculiarities among diabetics. Dietary and insulin control of hypercholesterolemia and of the derangement of carbohydrate metabolism in diabetes aid to some extent in retarding cardiovascular complications. On the other hand, an unintentional over-dosage of insulin involves grave cardiac hazards and must be carefully avoided.

Hyperinsulinism

The term "hyperinsulinism" in the strict sense refers to abnormal, excessive discharges of insulin from the pancreas and to the resulting syndrome. Hypoglycemia and ensuing central nervous, neurovegetative and cardiovascular reactions dominate the clinical picture. Beside this pancreatogenic form of "absolute" hyperinsulinism, there exist states of "relative" hyperinsulinism in which there is no evidence of an increased insulin secretion but in which hypoglycemia is induced by the temporary or constant deficiency of certain endocrine and neurohormonal factors which under normal circumstances participate as antagonists of insulin in the maintenance of homeostasis.

Endocrine Pathology

Absolute hyperinsulinism results, as a rule, from the insulin secretion of benign or malignant and metastasizing tumors of the islets of Langerhans which are usually located in the tail of the pancreas^{107, 108, 109, 110, 111, 112}. The responsibility of such adenomas for the clinical syndrome was first proven by Wilder in 1927¹⁰⁷. Most of them are small, varying from one to two cm in diameter. In some cases, no tumor was found at operation; yet symptomatic relief was obtained by subtotal resection of the pancreas^{113, 114, 115, 116, 117}, so that the existence of a functional hyperinsulinism without morphological pathology can be assumed¹¹⁸. A special type of pancreatic hyperinsulinism is that of infants born by diabetic mothers and harboring hyperplastic islets^{112, 119}.

The relative hyperinsulinism connected with Addison's disease and panhypopituitarism, is indirectly caused by the pathological lesions which were discussed in the respective sections (pp. 107 and 174).

The so-called "neurogenic hypoglycemia" may be provoked by an abnormally increased vagal tone^{120, 121}, either without underlying anatomical lesion¹²² or in connection with brain tumors, encephalitis, or brain injuries^{123, 124}.

A marked secondary hyperactivity of the adrenal medulla and cortex under the influence of insulin hypoglycemia has been proven by morphological and functional evidence (p. 50).

General Symptomatology; Diagnosis

of
The onset is often precipitated by vigorous physical exercise or periods of fasting, e.g., early in the morning or a few hours after a carbohydrate-rich meal, when the phase of post-hyperglycemic hypoglycemia sets in. The "spells" may last for minutes to hours. Their intensity is variable. It may be limited to moderate discomfort with pallor or flushing, dizziness, diplopia, paresthesias, nausea, epigastric pain, trembling, perspiration, palpitations, craving for food, weakness and speech impairment, but major attacks may assume very severe proportions with marked mental disturbances, epileptiform convulsions, prostration, and in extreme cases coma and death. The patients, many of whom are overweight, usually do not present any conspicuous abnormalities between attacks and do not retain any clear memory of the attacks themselves.

Systematic analysis of the symptoms made it plain¹²⁵ that deprivation

of the central nervous system of its necessary carbohydrate supplies is

50) which produce striking cardiovascular phenomena (p. 51).

The syndrome of hyperinsulinism is often mistaken for hysteria, epilepsy, brain tumor and other nervous disorders^{1754, 2099}, but even if the possibility of a pancreatic adenoma is thought of and the presence of hypoglycemia during attacks established, the differential diagnosis against other conditions associated with hypoglycemia is not easy. Fully developed panhypopituitarism or Addison's disease, severe under-nutrition and advanced liver disease can be ruled out without difficulty; but acute hypoglycemic episodes of central nervous origin³⁶¹⁷ may create a problem which to solve is all the more important, as the decision for or against abdominal surgery will depend on the diagnosis.

Moderately low blood sugar levels, a flat glucose tolerance curve and maintenance of a subnormal blood sugar level five and six hours after sugar ingestion are not sufficiently specific and may be too much affected by the preceding diet⁵⁷² to serve as differential diagnostic evidence by themselves^{812, 2221}. However, the following criteria will be helpful to identify true hyperinsulinism, (a) a blood sugar of less than 60 mg per cent during the post-absorptive period and of less than 50 mg per cent during attacks³⁶¹⁷; (b) intolerance to fasting and exercise, which will bring on typical attacks; (c) prompt abolition of the attack by intravenous administration of glucose; (d) a history of good health before onset of the disease and in between attacks. The patterns of reaction to the injection of small doses of insulin and to the intravenous application of glucose are also said to permit specific diagnostic conclusions²⁰⁹⁸.

Cardiovascular Manifestations

The cardiovascular symptoms connected with the syndrome of hyperinsulinism are essentially attributable to the discharges of sympathomimetic catecholamines from the adrenal medulla and possibly also from other sections of the sympathetic system, plus changes in cardiac carbohydrate metabolism, although the latter are probably of only minor importance, as discussed elsewhere (p. 50).

The mainly epinephrine-induced *increase in systolic blood pressure* and the even more regular *augmentation of pulse pressure* as well as of *cardiac output*, occurring during individual hyperinsulinic attacks, are as a rule not of a sufficient magnitude to cause immediate or lasting cardiovascular damage of a significant degree, as long as the myocardium and arteries are primarily in good condition²³⁴⁵. On the other hand, experimental observations regarding electrocardiographic and structural changes of the heart,

produced by insulin over-dosage (pp. 51 and 53), serve as an impressive warning that hypoglycemic episodes must not be taken lightly from the cardiovascular point of view. Serious cardiac complications must be expected from insulin-provoked epinephrine discharges in elderly persons and in those whose hearts were handicapped already before the onset of the disease, or in whom frequent severe attacks may have contributed to the gradual establishment of permanent cardiac damage. Conclusions regarding potentially detrimental clinical effects of insulin are based predominantly upon observations made on insulin-treated diabetics and insulin-shocked schizophrenic individuals, but there is no reason to doubt that they are also applicable to the spontaneous attacks of pancreatic hyperinsulinism. Anginal symptoms, for instance, have been described as a characteristic feature of spontaneous hypoglycemia^{118, 112}.

In mostly elderly diabetic and arteriosclerotic patients, marked changes of the ECG (depression of S-T and T, prolonged Q-T, intraventricular block, extra-systoles, auricular fibrillation)^{124, 125, 126} have been recorded under therapeutic administration of insulin and in a number of cases severe anginal attacks, pulmonary edema, signs of myocardial infarction and death occurred as apparent results of insulin treatment^{127, 128, 129, 130, 131, 132}. Similar accidents were also seen under the influence of large shock doses in mental patients^{133, 134}.

In an interesting study based on meticulous clinical observations, Harrison and Finks (1943)¹³⁵ have presented rather conclusive evidence for the not infrequent occurrence of symptoms referable to "relative hypoglycemia", i.e., to a state of mild glucose deficiency, supervening in hypertensive, menopausal, neurotic and other patients after meals at the time when the post prandial "Staub effect" (secondary insulinemia, accompanied by counter-regulatory epinephrine discharge) is in operation. The symptoms consisted of nervousness, weakness, anxiety and blurring of vision as the expressions of cerebral carbohydrate depletion and of typical epinephrine reactions, such as tachycardia, increased pulse pressure "pistol shot sounds" over the arteries, capillary pulsation, and anginal pain. They could usually be duplicated by injection of small doses of insulin, relieved by ingestion of glucose and prevented by the use of a low-carbohydrate, high-protein diet. The authors ascribe the cardiovascular phenomena of this syndrome to a dual mechanism of "both anoxia and epinephrine". However, in the light of present-day knowledge, such a separation is no longer necessary and justified, since the powerful myocardial hypoxia-producing effect of epinephrine itself has been recognized as a well established fact (p. 115f.) of paramount importance for various features of cardiac pathology.

No systematically collected data seem to be available regarding cardiovascular reactions to "relative" hyperinsulinism and hypoglycemia in cases

of Addison's disease and panhypopituitarism; but in view of the generally lesser responsiveness to epinephrine which prevails in such conditions, one would expect a less prominent participation of sympathicotonic cardiovascular manifestations, even in the presence of severe central nervous derangements, caused by carbohydrate depletion.

Post-mortem reports concerning heart and blood vessels of patients who have succumbed to pancreatic or artificially induced hyperinsulinism are scarce and inconclusive, as far as a causal connection of demonstrable changes with insulin over-action is concerned. Findings of cerebral edema and hyperemia^{120 2018, 3363, 3506} seem to be more specific and perhaps due to a direct influence of insulin on brain circulation and metabolism.

Treatment

Whenever diagnostic studies have established the presence of pancreatic hyperinsulinism with reasonable certainty, an exploratory laparotomy and, if possible, *removal of the tumor* or tumors should be performed. This should be done not only for the purpose of symptomatic relief, but also in order to prevent gradual damage to the central nervous and cardiovascular systems and in order to evade the possibility of malignant degeneration. The operative procedure may prove a difficult task because of the smallness, occasional multiplicity or invisibility of the adenomas, which may be deeply imbedded in the parenchyma of the pancreas. If surgery seems contraindicated or remains unsuccessful, conservative treatment must be attempted. Its most important rules concern the *avoidance* of situations which are likely to precipitate attacks, i.e., *strenuous physical exercise, long periods of fasting and the intake of large meals rich in rapidly absorbable carbohydrates. A low-carbohydrate and high-protein diet*⁷² *with ample fat*, (except in the presence of obesity) distributed in about six small meals over the day,¹⁶⁸⁰ is likely to protect the patient from excessive post-prandial insulin discharges. However, if an attack is under way, the immediate *ingestion of sugar, candy, fruit juice and the like*, or in case of unconsciousness, intravenous injection of hypertonic glucose solution will quickly restore normal conditions. Patients afflicted with this disease should always carry a tag with instructions for first aid assistance so that proper treatment can be applied at once in case of emergency.

Sedatives for the mitigation of central nervous reactions and nitroglycerin for anginal pain may be of limited symptomatic usefulness. Epinephrine in oil has been suggested¹⁶⁸⁰ as a potential antagonist against the metabolic effects of insulin, but seems inadvisable as far as cardiovascular complications are concerned. The administration of alloxan^{412 3313} was a theoretically interesting idea and gave transient relief, but seems to be too dangerous for general clinical use¹⁶⁸⁰.

Injectons of ACTH are reported as having been helpful in a few cases so far.^{2162, 2166} Further experiences with this rationally well-enough founded form of treatment must be awaited. Cortisone may be tried for similar reasons.

Heuristic Aspects of the Cardiovascular Manifestations of Hyperinsulinism

In view of their causation by secondary discharges of epinephrine (and possibly nor-epinephrine?), the cardiovascular phenomena connected with attacks of pancreatogenic as well as of artificially induced insulin hypoglycemia serve as another instructive example of the adenosympathogenic neurosecretory mechanisms through which myocardial hypoxia can be elicited. Although usually less violent than those originating from pheochromocytomas, the sympathomimetic discharges provoked by insulin are associated with the characteristic electrocardiographically demonstrable myocardial hypoxia and resulting anginal pains, which constitute the typical effect of the hypoxiating adenosympathogenic catecholamines upon the heart muscle (in 1167). It may well be that

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carbohydrate supply for myocardial function (p. 50), only minor significance may have to be attached to this factor.

Analogous cardiac phenomena can apparently be provoked in sensitive individuals and in those with coronary sclerosis, by physiologic post-prandial insulin discharges and accompanying adenosympathetic neurosecretion.

Summary

The neurovegetative, mental and cardiovascular syndrome which develops acutely during attacks of pancreatogenic hyperinsulinism as well as in association with artificial insulin over-dosage, is in part due to central nervous carbohydrate depletion, in part to secondary (central) adenosympathetic

changes. Similar milder effects can occur in sensitive individuals under the influence of physiological post-prandial insulin and epinephrine discharges.

The "relative" hyperinsulinism in cases of pituitary or adrenal cortical deficiency is less likely to cause adenosympathogenic cardiovascular disturbances.

Parathyroids

Hyperparathyroidism

Endocrine Pathology

The causation of "osteitis fibrosa cystica generalisata von Recklinghausen" by an over-production of the parathyroid hormone was directly proven by Mandl in 1926³¹⁹³. The underlying disturbance consists in the majority of cases of an adenoma, usually benign, of one of the four parathyroid glands or of aberrant parathyroid tissue, e.g., in the mediastinum; in a minority of cases, the disease is caused by hyperplastic or hypertrophic changes of the parathyroids^{319, 3114, 3263}. Women are more frequently affected than men and clinical manifestations occur mostly during adult life between the 20th and 60th year.

General Symptomatology; Diagnosis

Because of the vagueness of its general symptoms, such as loss of appetite and weight, weakness, paresthesias, diffuse aches, constipation, nausea and polyuria, the condition often remains unrecognized for a long time until a spontaneous "pathological" fracture or a renal colic provides the occasion for x-ray studies which will reveal characteristic bone lesions: cyst-like localized areas of decalcification of the long bones, or more generalized calcium depletion, mottled appearance of the calvaria, pelvic bones, etc., and besides, often calcium deposits in soft tissues, particularly in the kidneys and lower urinary passages with formation of calculi. Renal excretory failure may supervene, especially in cases of long standing. In untreated cases, death used to be precipitated by multiple deforming bone fractures, general debility, infections, sarcomatous degeneration of the bone "cysts", and uremia.

The outstanding metabolic derangements, which account for most of the above-named manifestations, consist of an excessive mobilization of calcium from the bones, probably caused by parathormone-induced stimulation of osteoclastic activity, hypercalcemia, increased urinary calcium excretion, hypophosphatemia, and increased serum phosphatase activity.

For diagnostic purposes, determination of the *blood calcium level* is of decisive significance. The values may rise as high as 20 mg per cent. However, in the case of co-existing hypoproteinemia, the total calcium readings may remain within normal limits because the ionized blood calcium is usually balanced against the amounts of protein-bound calcium. In case of

doubt, it is necessary to determine the plasma proteins in order to eliminate this source of error in the interpretation of ultrafilterable calcium readings²³.

The *inorganic phosphorous level* is found near or below the lower limits of normal (2.5 mg per cent in adults, 4.5 mg per cent in children) and alkaline phosphatase is, as a rule, increased above the upper normal value of four Bodansky units.

Röntgen examination of the skeleton and kidneys discloses in most instances the characteristic findings of decalcification of the former and calcification of the latter.

Cardiovascular Manifestations

Among 32 cases of hyperparathyroidism, *systolic blood pressure* levels higher than 140 mm were observed in 56.3 per cent, but although this percentage supports the "clinical impression" of a tendency toward hypertension, it cannot be considered as statistically significant²⁰⁶. Since secondary renal involvement is a common feature in hyperparathyroidism, it must be assumed that some of the cases of hypertension in this group of patients originated on a renal basis and cannot be attributed directly to overactivity of the parathyroid hormone.

In accordance with the fact that . . .
is associated with a *shortening of the* . . .
was found diminished in patients w
toward its normal dimensions after . . .

and *ventricular conduction* and *shorted ventricular complexes* were also occasionally seen²⁰⁹.

There are certain similarities in the cardiac actions of calcium on one hand and the digitalis glycosides on the other^{210, 211}. The intensification of the cardiac effects of strophanthin by calcium^{207, 212}, as indicated by a diminution of the fatal dose of strophanthin and of the dose necessary to produce idioventricular beats, in hypercalcemic animals²¹³, suggests caution in the use of digitalis in the presence of hypercalcemia^{208, 214, 215}.

The occasion for an administration of digitalis in hyperparathyroid patients may arise in connection with cardiac failure, resulting from severe calcium-induced renal damage and insufficiency.

Morphological Cardiovascular Lesions

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the presence of extensive calcium deposits

in vascular walls and myocardium, as well as in various other tissues of such patients. Yet, it is said that arteriosclerosis does not appear to be a regular complication of von Recklinghausen's disease¹²⁶⁵.

Treatment

The only effective treatment for hyperparathyroidism is surgical removal of the tumor²¹⁹⁹ or, in case of simple hyperplasia, of three parathyroid glands⁵²². If this is performed before the establishment of irreparable damage to the skeleton or kidneys, normal conditions will be restored. Roentgen irradiation proved ineffective¹⁶⁷⁸ with only few exceptions¹⁶⁴⁰. It may be tried if surgery remains unsuccessful.

Heuristic Aspects of the Cardiovascular Manifestations of Hyperparathyroidism

In view of the general rarity of hypercalcemia, which is responsible for the electrocardiographic manifestations occurring in hyperparathyroidism, this endocrine disease offers but little information which would be useful in the evaluation of pathogenic mechanisms contributing to other forms of cardiovascular pathology. Significant functional cardiac disturbances do not seem to result directly from parathyroid over-function. Calcium deposits in the heart muscle, arterial walls and kidneys are of a secondary nature and pathogenically probably not comparable to the calcification of vascular walls in common arteriosclerosis.

The hypothesis that the cardiac action of the digitalis glucosides might be due to sensitization of the heart muscle to the effects of calcium²⁰⁷⁶ has been disproved^{1539 2196 2437}

Summary

The heart is affected by hyperparathyroidism insofar as the resulting hypercalcemia gives rise to a shortening of the electrical systole (Q-T). Renal calcinosis, calcifications of arterial walls and of the myocardium may lead to secondary cardiac lesions

Hypoparathyroidism (Tetany)

Endocrine Pathology

Under-function of the parathyroid glands may occur after thyroidectomy due to the unintentional surgical removal or injury of more parathyroid tissue than is compatible with maintenance of a normal calcium-phosphorus metabolism. A similar situation arises occasionally after excision of a para-

cases of "idiopathic" tetany, local inflammation or hemorrhage of the parathyroid glands is assumed to cause their functional deficiency. Scars, cysts, or atrophy of the glands were occasionally observed¹⁶⁷, but many cases remained entirely unexplained. Beside those forms of tetany which are caused by an absolute decrease of parathyroid secretion, there are other essentially non-endocrine conditions which share with them the clinically decisive phenomenon, namely a diminution of ionized calcium in the blood and the corresponding neuromuscular signs^{168, 169}. Such an alteration of the blood calcium occurs in the presence of normally functioning parathyroids if excessive vomiting or hyperventilation produces alkalosis which causes a reduction of ionized calcium in the blood. Severe diarrheas, sprue, celiac disease and Vitamin D deficiency may lead to tetany because of impaired intestinal calcium absorption. Tetany, which occurs during the period of lactation, has been attributed to an excessive loss of calcium with the milk. Such conditions one might describe as "relative hypoparathyroidism", in that the parathyroid glands fail to replenish the depressed levels of ionized blood calcium by mobilizing sufficient amounts of calcium from the bones. Tetanic symptoms occurring in patients with congenital or acquired cerebral lesions and injuries¹⁷⁰ and under emotional stress (with or without hyperventilation)¹⁷¹ seem to be caused by exaggerated neuromuscular responses to sympathetic stimuli.

General Symptomatology

Characteristic "carpopedal" spasms of the hands and feet, lasting for minutes to hours, spastic contractions of the perioral muscles, squinting, and especially in children, laryngeal and bronchial spasms, are caused directly by the deficiency in ionized calcium. Swallowing is usually possible because:

route normal 3-5

Chronic parathyroid tetany. It may also be associated with psychic irritability or psychotic states.

A decrease of the blood calcium level constitutes the most conspicuous chemical anomaly, but it is not always manifest in between attacks and the total blood calcium readings (normal 8-11 mg per cent) do not always reflect the concentration of ionized calcium. Urinary calcium excretion is low or temporarily absent. The blood level of inorganic phosphorus is usually higher than 3.5 mg per cent in adults and higher than 6.0 mg per cent in children, but there are exceptions to this rule. The Ca-P ratio in the serum is decreased. Phosphatase activity is not significantly altered. Chvostek's, Trousseau's and Erb's signs, indicating increased neuromuscular excitability, are diagnostically useful in the intervals between attacks.

Cardiovascular Manifestations

A *prolonged Q-T interval*, the counterpart to the short Q-T of hyperparathyroidism, constitutes a characteristic peculiarity of the tetany syndrome^{148, 151, 2239, 2506, 2601} and indeed has been recommended by some workers¹⁰⁵¹ as a sign of a certain diagnostic value. In cases of tetany, it is caused by the depression of the blood calcium; but it is also occasionally seen in other conditions with a lowered blood calcium level, such as renal failure with uremia¹⁴⁹ or in certain cardiac lesions of an entirely different nature¹⁰⁶⁰. The prolongation of the electrical systole is not always paralleled by an equal prolongation of the mechanical systole, as estimated by the recorded heart sounds¹⁴⁹. Therapeutic normalization of the blood calcium level is followed by reduction of the Q-T interval to its normal size^{149, 2506, 2601}.

Other electrocardiographic changes, such as shortened P-R intervals and QRS complexes, have been described^{737, 1426, 2376}, but are too irregularly seen to be considered as definitely characteristic for tetany²⁹²². A flattening of the T-wave, as observed in hyperventilation tetany with alkalosis^{148, 151, 2119}, seems to correspond to an analogous reaction, induced by sodium bicarbonate alkalosis¹⁴⁵.

An exaggerated contractile response of the vessels of the hand to injection of epinephrine into the brachial artery¹⁴⁰⁵ as well as accentuated general pallor and tachycardia have been produced by small epinephrine doses in tetany patients^{846, 947}. These reactions were interpreted as being due to an *abnormal sensitization of the cardiovascular system to the epinephrine stimulus* because of a reduction of available calcium in the environment and a resulting alteration of the K-Ca ratio^{1405, 1642}. An increased tension of the arterial wall in persons with "spasmophilia" has been claimed on the grounds of comparative measurements²⁵⁷⁷. Clinical observations of the blood pressure in two series of patients with tetany (25 and 51 cases respectively^{2519, 2937}) did not reveal any consistent abnormality, however.

Anginal symptoms are said to be a not uncommon feature in tetany patients¹⁶⁷³ and, on the other hand, treatment of angina pectoris with parathyroid extract was claimed to have given some symptomatic relief in a few preliminary observations¹³⁵⁹. *Sudden death*, occasionally occurring in children afflicted with tetany, was attributed to the intensified cardiac action of suddenly discharged epinephrine¹⁰⁰⁸, a conception which seems to be indirectly supported by the writer's own findings of an excessive accumulation of epinephrine-like substances in the hearts of persons who had suddenly died without any other demonstrable pathological condition^{2674, 2677}. Tetanic spasms of the striated muscles are likewise provoked with unusual ease in persons with a low function level of the parathyroid glands ("latent tetany") by injection of epinephrine⁸²², or by the epinephrine discharges accompanying emotional tension and anxiety¹⁴⁰⁶. The co-existence of cardio-

vascular over-sensitivity to epinephrine with an abnormal readiness to develop tetanic spasms during hyperventilation or in connection with diarrhea (dysentery) is known to the writer from personal experience.

Treatment

The foremost therapeutic goal in hypoparathyroid tetany is restoration of the calcium balance. This can be achieved by injections of parathyroid hormone, but is more conveniently done either by the oral (during attacks, if necessary, intravenous) administration of calcium salts, especially calcium gluconate (10 grams or more per day), or by oral medication with the slow acting but very effective dihydrotachysterol (AT10) in oil (2-6 mg per day in the beginning, followed by maintenance with 2-4 mg per week). This substance mimics the bone calcium-mobilizing and intestinal calcium absorption-favoring actions of parathormone. Over-dosage can be avoided with the aid of the Sulkowitch test¹² which reveals the appearance of excess calcium in the urine. Phosphorus should be restricted in the diet by reducing the intake of meat, egg yolk, cheese, etc. Vitamin D₂ (calciferol) is particularly useful in children.

Heuristic Aspects of the Cardiovascular Manifestations of Hypoparathyroidism

The increased sensitivity of some sections of the vascular system and of the heart to epinephrine which has been observed in individuals with manifest or latent tetany is an interesting phenomenon with possible far-reaching consequences.

As the symptoms and sudden deaths which occasionally occur in tetany patients are precipitated by calcium deficiency, it might be worthwhile to pay more attention to calcium metabolism also in non-hypoparathyroid cases of angina and sudden death.

Summary

A prolongation of the electrical cardiac systole (Q-T), which is caused by hypocalcemia, constitutes a rather regular cardiac manifestation in hypoparathyroid tetany. Cardiac and peripheral vascular sensitivity to epinephrine seems to be increased in hypoparathyroidism.

SYNOPSIS OF Cardiovascular Features in Endocrine Syndromes

In the following tables (nos 8, 9, 10, 11), the occurrence of various cardiovascular features in the most important endocrine syndromes is indicated

SYMBOLS

⦿ increased, ⦿ decreased, + present fairly regularly and/or to a major degree;

† increased, † decreased, + present frequently and/or to a moderate degree;

(†) increased, (†) decreased, (+) present occasionally and/or to a minor degree.

The tables include only cardiovascular changes which can be assumed to be caused directly or indirectly by endocrine action. Modifications of pre-existing cardiovascular diseases by endocrine factors are not included (except for the probable aggravation of arterio-sclerosis by diabetes mellitus).

The cardiovascular manifestations of "Cushing's disease" of problematic pituitary origin are represented under the heading "Adrenals" because of their identity with those of primarily adreno-cortical "Cushing's syndrome".

The heading "Pancreas" comprises also forms of diabetes mellitus, the primary disturbance of which may be located conceivably in the pituitary and cortex rather than in the pancreas itself

TABLE 8

Blood Pressure, Hemodynamics and Electrolytes (Na⁺) in Endocrine Syndromes

GLAND	ENDOCRINE SYNDROMES	BLOOD PRESSURE		STROKE VOLUME	CARD OUTPUT	CIRCULATORY VOLUME	Na ⁺ IN BLOOD	HORMONE SECRETION			REMARKS
		Syst.	Diast.					Catecholamines	Mineralocorticoids	Thyroid hormone	
Adrenals	Phaeochromocytoma	⬆	⬇					⬆	+		* Paroxysmal or sustained flow diastolic pressure if epinephrine prevalent over nor-epinephrine † Secondary increase
	Hyperadrenocorticism (Cushing's syndrome)	⬆	⬆				⬆	(1)*	⬆		* Slight increase of catecholamines in blood (possibly due to impaired renal excretion) Pressure effect of catecholamines potentiated by corticoids
	Hypoadrenocorticism (Addison's disease)	⬆	⬆	⬆	⬆	⬆	⬆	•	⬆		* Pressure effect of catecholamines decreased due to lack of corticoids
Thyroid	Hyperthyroidism	(1)	⬆	⬆	⬆	(1)		•		⬆	* Cardiac effects of catecholamines, esp. of epinephrine potentiated by thyroid hormone
	Hypothyroidism			⬆	⬆	(1)		•		⬆	* Cardiac effects of catecholamines esp. of epinephrine weakened due to lack of thyroid hormone
Pituitary	Acromegaly	(1)							(1)*		* Mineralocorticoids not specifically assayed but total corticoids sometimes increased (growth hormone increased)
	Hypopituitarism (Pituitary disease)	1	1				1		1*	1†	* Secondary hypoadrenocorticism † Secondary hypothyroidism
Gonads	Pregnancy (not toxemia)	(1)*	1	↑	↑	⬆	↑*		↑†		* In toxemia † Total corticoids increased, esp. in toxemia (partly of fetal origin) Gonadotrophins, estrogens, progesterone increased
	Menopausal syndrome Castration	(1)							•		* Corticoids probably increased Gonadotrophins increased

SYNOPSIS OF Cardiovascular Features in Endocrine Syndromes

In the following tables (nos. 8, 9, 10, 11), the occurrence of various cardiovascular features in the most important endocrine syndromes is indicated

SYMBOLS

⌘ increased, ⌘ decreased, + present fairly regularly and or to a major degree;

† increased, † decreased, + present frequently and/or to a moderate degree,

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TABLE 9

Heart Rate, ECG, Heart Size (X-ray), and Oxygen Consumption in Endocrine Syndromes

GLAND	ENDOCRINE SYNDROMES	HEART RATE	ELECTROCARDIOGRAM					HEART SIZE (X RAY)	HORMONE SECRETION			REMARKS	
			Voltage	P	ST	T	QT		RM/R	Catecholamine	Mineralocorticoids		Thyroid hormone
Adrenals	Pheochromocytoma	↑ (↓)*		(↑)	(↓)†	↓†	(↑)	↑	⊕	⊕	↑	*Bradycardia sometimes during paroxysms †Mainly during paroxysms ‡Possibly secondary increase	
	Hyperadrenocorticism (Cushing's syndrome)	(↑)			(↓)	↓		↑	(↑)	(↑)*	⊕	*Slight increase in blood (possibly due to impaired renal excretion)	
	Hypoadrenocorticism (Addison's disease)	↓	(↓)		(↓)*	(↓)*	(↑)	⊖	↓	↓	⊖	*Especially during crises. †Cardiac effects of catecholamines decreased due to lack of corticoids	
Thyroid	Hyperthyroidism	⊕	↑	↑	(↑)*	↑	↑*	↑	⊕	↑		⊕	*Depressed mainly in advanced cases with myocardial damage †Cardiac effects of catecholamines, esp. of epinephrine, potentiated by thyroid hormone
	Hypothyroidism	↓	⊖	⊖	(↓)*	⊖		↑†	⊖	↓		⊖	*In case of coronary atherosclerosis †Partly myocardial edema partly pericardial effusion. ‡Cardiac effects of catecholamines weakened due to lack of thyroid hormone
Pituitary	Acromegaly				(↓)	(↓)		⊕	↑*		(↑)†		*Not of thyroid origin cause unknown †Mineralocorticoids not specifically assayed but total corticoids sometimes increased (Growth hormone increased)
	Hypopituitarism (Simmonds' disease)	↑†	↑†					↓*	⊖†		↓*	↑†	*Secondary hypoadrenocorticism. †Secondary hypothyroidism

TABLE 8—Continued

CLAND	ENDOCRINE SYNDROMES	BLOOD PRESSURE		STROKE VOLUME	CARD OUTPUT	CIRCULATORY VOLUME	Na ⁺ IV BODY	HORMONE SECRETION			REMARKS
		Syst.	Diast.					Catecholamines	Mineralocorticoids	Thyroid hormone	
Pancreas	H ₂ perinsulinism attacks (spontaneous and induced)	↑	↓	↑				↑*			*Secondary discharge of epinephrine (and norepinephrine?)
	Diabetes mellitus	↑*									*Probably due to increased pituitary-cortical activity
Parathyroids	H ₂ hyperparathyroidism	(↑)*									*Probably due to renal pathology

TABLE 10

Anginal Symptoms, Congestive Heart Failure and Morphological Cardiovascular Lesions in Endocrine Syndromes

























GLAND	ENDOCRINE SYNDROMES	CARDIAC SYMPTOMS		POST MORTEM FINDINGS					HORMONE SECRETIONS			REMARKS
		Angina pectoris	Congestive heart failure	Atherosclerosis	Arteriosclerosis	Heart weight	Coronary sclerosis	Myocardial lesions	Catecholamines	Mineralocorticoids	Thyroid hormone	
Adrenals	Phenochromocytoma	+	(+)	+	+	重	(+)	(+)	重	+		*Possibly secondary increase of corticoids
	Hyperadrenocorticism (Cushing's syndrome)	+	+	+	重	+	+	+	(+)*	重		*Slight increase of catecholamines in blood (possibly due to impaired renal excretion)
	Hypoadrenocorticism (Addison's disease)				重			+*	+	重		*Atrophy (Cardiac effects of catecholamines decreased due to lack of corticoids)
Thyroid	Hyperthyroidism	(+)	(+)			+		+	+		重	*Cardiac effects of catecholamines, esp. of epinephrine, potentiated by thyroid hormone
	Hypothyroidism	(+)*	(+)*	+		++	+	++	+		重	*In cases of coronary sclerosis, myocardial edema and coronary sclerosis ?Cardiac effects of catecholamines weakened by lack of thyroid hormone
Pituitary	Acromegaly	+	+	+	重	+	+	+		(+)*		*Total corticoids sometimes increased (Growth hormone increased)
	Hypopituitarism (Simmonds disease)									+	++	*Secondary hypoadrenocorticism ?secondary hypothyroidism
Gonads	Pregnancy (incl. toxemia)		(+)*			(+)		++		++		*In toxemia, ?Myocardial edema in toxemia ?Total corticoids increased (esp. in toxemia) (Gonadotropins, oestrogens, progesterone increased)
	Menopausal syndrome (castration)	(+)*		(+)(+)						+		*Possibly not true angina ?Not caused but accelerated by hypogonadism ?Corticoids probably increased (Gonadotropins increased)
Pancreas	Hyperparathyroidism attacks	+							+			*Secondary discharge of epinephrine
	Diabetes mellitus	(+)*	(+)(+)	++	++	(+)(+)	++	++				*In case of aggravated coronary sclerosis ?Probably aggravated by pituitary-cortical activity
Parathyroids	Hyperparathyroidism			+								*Calcifications
	Hypoparathyroidism	(+)*										*Increased sensitivity to epinephrine

TABLE 9—Continued

GLAND	ENDOCRINE SYNDROMES	HEART RATE	ELECTROCARDIOGRAM					HEART SIZE (X-RAY)	BMR	HORMONE SECRETION			REMARKS
			Voltage	P	S-T	T	Q-T			Catecholamines	Mineralo-corticoids	Thyroid hormone	
Gonads	Pregnancy (incl. toxemia)	↑						(↑)	⊕*		↑↑		*Due to uterine and fetal tissue ↑Total corticoids increased, esp. in toxemia (Gonadotrophins, estrogen and progesterone increased)
	Menopausal syndrome, Castration	(↑)			(↓)	(↓)					*		*Corticoids probably increased (Gonadotrophins increased)
Pancreas	Hyperinsulinism attacks	↑			↓	↓	↑			↑*			*Secondary discharges of epinephrine
	Diabetes mellitus				↓*	↓*	(↑)*						*In case of aggravated coronary sclerosis and hypertension
Parathyroids	Hyperparathyroidism						↓*						*Due to hypercalcemia
	Hypoparathyroidism						↑*						*Due to hypocalcemia

TABLE II
Etiological Therapy, Directed against Endocrine Syndromes and Their Cardiovascular Complications

GLANDS	ENDOCRINE SYNDROMES	NON-SURGICAL PROCEDURES	SURGICAL PROCEDURES
Adrenals	Pheochromocytoma	Adrenolytic drugs during paroxysms and for prevention	Removal of tumor
	Hyperadrenocorticism (Cushing's syndrome)	X-ray irradiation of adrenals and pituitary, testosterone, estrogens	Removal of cortical tumor or bilateral adrenalectomy followed by permanent substitution with cortical extracts
	Hypoadrenocorticism (Addison's disease)	Deoxycorticosterone acetate, cortisone, corticosterone, cortical extracts, NaCl During crises: Cortical extracts, saline, glucose i.v.	
Thyroid	Hyperthyroidism	Propyl- or methylthiouracil, radioiodine	Thyroidectomy, esp. in case of adenomatous goiter
	Hypothyroidism	U.S.P. thyroid, beginning with small doses (in pituitary myxedema) combined with corticoids, ACTH	
Pituitary	Acromegaly	X-ray irradiation of pituitary area, radon seeds in sphenoidal sinus	Removal of pituitary adenoma
	Hypopituitarism (Simmonds' disease)	ACTH, adreno-cortical extracts, testosterone, estrogens, thyroid hormone, NaCl	
Gonads	Orchitis		
	Castration	as in orchitis, testosterone, diethylstilbestrol, testosterone, psychotherapy	
Pancreas	Hyperinsulinism	During attack: sugar by mouth or i.v. Preventive: Low carbohydrate, high protein, high fat diet, multiple small meals, avoidance of strenuous exercise and of fasting	Removal of islet cell tumor
	Diabetes mellitus	In cardiovascular cases: dietary treatment preferable to insulin, if insulin necessary avoid hypoglycemia, give high carbohydrate-low caloric diet	
Parathyroids	Hyperparathyroidism	If surgery unsuccessful: x-ray irradiation of thyroid region (usually ineffective)	Removal of parathyroid tumor or of 3 parathyroids
	Hypoparathyroidism	Calcium gluconate or lactate daily, desmopressin, parathormone, restriction of phosphorus in diet	

CLIN. ENTITY	HEART	ECG.	BL. PR.	ARTERY ARTERIOLE	B.M.R.
PHEOCHROMOCYTOMA					+60%
CUSHING'S SYNDROME					+35%
ADDISON'S DISEASE					-15%
THYROID TOXICOSIS					+50%
MYXEDEMA					-35%
ACROMEGALY					+30%

activities

III

ENDOCRINE AND NEUROENDOCRINE FACTORS IN CARDIOVASCULAR SYNDROMES

IIII

ENDOCRINE AND NEUROENDOCRINE FACTORS IN CARDIOVASCULAR SYNDROMES

Introduction

Before venturing into the discussion of the role of endocrine and neurohormonal factors in the pathogenic mechanisms and therapeutic responses of several of the most common and most important cardiovascular syndromes, the writer wants to emphasize that it is the following section which represents the ultimate purpose of this book. It is intended to stimulate among medical readers and workers a definite trend of thought which, in the writer's opinion, forms a necessary prerequisite for a clearer understanding of some of the perplexing problems of cardiovascular disease.

In the preceding sections it was shown that certain neurohormonal and hormonal pathological syndromes involve functional and structural cardiovascular disorders of all degrees from slight to fatal, and analogies with common forms of cardiovascular disease were alluded to. It will be the aim of some of the following chapters to examine the question as to whether and to what extent such analogies are only superficial and accidental or indicative of a more intimate causal relationship than is generally assumed. There are probably only few cardiologists who may have remained unaware of the vast number and significance of observations scattered throughout the international literature which forcefully suggest the widespread, potentially pathogenic interference of endocrine factors in the cardiovascular system, but it is one thing to admit the existence of certain facts, and another thing to incorporate them as integral tools into one's daily reasoning.

In the following paragraphs, a number of basic features and conceptions, derived from Sections I and II, will be pointed out as guiding principles in order to facilitate for the reader the absorption of much that will be

upon the heart muscle consists of an excessive wasteful oxygen consumption, resulting in a potentially injurious myocardial hypoxia. This myocardial hypoxia is normally prevented by the opposite metabolic effect of vagal neurosecretion. It will occur, however, when an imbalance between adrenergic and vagal counter-regulation exists, the former

work as the
heart muscle

exception, the crucial fact is disregarded that in the presence of even an

increased coronary flow and in the absence of a significant increase of cardiac work, marked myocardial hypoxia can be elicited by epinephrine and by sympathetic stimulation (essentially identical with a local discharge of nor-epinephrine) as a purely biochemical neurohormonal phenomenon. The reader is urged to study carefully figures 49 and 50 and their legends which illustrate a fundamental principle of neurohormonal cardiac physiopathology, namely chemically induced myocardial hypoxia.

(2) Epinephrine and nor-epinephrine are not, as one might think after perusal of many clinical textbooks, merely "drugs", produced exclusively by the pharmaceutical industry and without major clinical significance. On the contrary, they are extremely potent, rapidly acting physiological agents which are secreted in part by the adrenal medulla into the blood circulation, in part by the postganglionic sympathetic fibers directly into the contractile cells of the cardiovascular system where they are constantly present in relatively large and potentially toxic quantities.

(3) The cardiac, hemodynamic and metabolic effects of the thyroid hormone in the cardiovascular system are probably mediated by its greatly intensifying influence upon local metabolic and dynamic catecholamine action in the cardiovascular tissues.

(4) The mineralocorticoids of the adrenal cortex (experimentally represented by desoxycorticosterone acetate), if present in excess or if unopposed by a sufficient amount of antagonistic glucocorticoids, exert functionally and structurally injurious effects upon the muscular elements of the cardiovascular system. They tend to reduce renal excretion of sodium, but probably the most important potentially pathogenic significance of the mineralocorticoids rests in their unique ability to increase the intracellular sodium concentration.

(5) The degree of pressor efficiency of the sympathomimetic catecholamines, epinephrine and nor-epinephrine, depends on the action of mineralocorticoids, probably in proportion to their effect upon intra- and extracellular electrolyte distribution and resulting magnitude of the electrical membrane potential of the contractile cells. Uncontrolled mineralocorticoid action would thus produce hypertension essentially by sensitizing the vascular cells to the contraction stimulus of the ubiquitous depolarizing adrenosympathetic catecholamines, lack of these corticoids would lead to hypotension by reducing the contractile reactivity of the vascular cells to the adrenosympathetic catecholamines.

(6) Epinephrine and nor-epinephrine are excreted with the urine in a prevailingly inactive, conjugated form in relatively large quantities. Their contact with the renal vessel walls during the process of excretion may constitute a danger of local toxic action for these vessels. On the other hand,

their retention in the circulation in states of renal excretory failure gravely threatens the cardiovascular system functionally and structurally.

(7) The process of cardiac hypertrophy and damage seems to be less dependent on the mechanical "burden" of peripheral circulatory resistance than is generally realized. It can be provoked by purely hormonal chemical influences, probably involving the growth hormone, the thyroid hormone and adrenal corticoids, without any definitive relation to dynamic performance. One of its prerequisites seems to be an increased local oxygen consumption, such as that elicited by the adrenosympathetic catecholamines, regardless of the degree of cardiac work or coronary flow.

Finally, it must be re-emphasized that wishful teleological but non-biological thinking which blurs the issues of cause and effect by imputing elements of "purpose", may not be entirely avoidable as a stop-gap in the discussion of phenomena whose origin and causal connections are completely obscure, but its scientific illegitimacy should never be lost sight of; it must never be considered as an ultimately acceptable means of explaining anything, and it must be discarded at once in each instance when reasonably proven facts become available to replace it. The writer has tried to adhere to these rules in the preceding chapters and will continue to do so in the following, in deliberate opposition to some current teleological clinical interpretations of cardiovascular functions and derangements.

In the discussion of the pathogenic role of hormones in various common forms of cardiovascular disease, an attempt will be made to apply the facts and concepts gathered from experimental observations and from the behavior of the cardiovascular system in clear-cut endocrine syndromes, to conditions whose hormonal background is less conspicuous and therefore largely overlooked but none-the-less a tangible reality. The writer realizes that many of his views differ from traditional concepts and he expects to be branded as a *hormonomaniac* but, although he cannot hope to be right in all of his interpretations and speculations, he is firmly convinced of following the right direction to struggle out of the dead-end street of exclusively mechanistic thinking in matters of cardiovascular pathology and therapy.

increased coronary flow and in the absence of a significant increase of cardiac work, marked myocardial hypoxia can be elicited by epinephrine and by sympathetic stimulation (essentially identical with a local discharge of nor-epinephrine) as a purely biochemical neurohormonal phenomenon. The reader is urged to study carefully figures 49 and 50 and their legends which illustrate a fundamental principle of neurohormonal cardiac physiopathology, namely chemically induced myocardial hypoxia.

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(6) Epinephrine and nor-epinephrine are excreted with the urine in a prevailingly inactive, conjugated form in relatively large quantities. Their contact with the renal vessel walls during the process of excretion may constitute a danger of local toxic action for these vessels. On the other hand,

lum consist of (a) a simple thickening, due to endothelial hyperplasia, (b) hyaline degeneration, (c) fibrosis, (d) lipoidosis and (e) calcification. Intimal thickening, hyalinosiis and fibrosis have been interpreted as the result of abnormalities of the intravascular hydrostatic pressure, caused by changes either of vascular tonus or of vascular filling, and as being enhanced by alterations of the protein composition of the blood plasma¹⁵⁹⁵. Intima lipoidosis, the substrate of so-called atheromatosis, accounts for the most conspicuous grossly discernible disfigurations of the inner surface of the larger arteries, giving rise to thrombus formations and occasionally to more or less complete occlusions of the vascular lumen.

It is almost unanimously agreed that intimal lipid depositions are not a primary process but require for their occurrence a preceding preparatory alteration of the intimal endothelium^{706 1913 2331}. For the penetration of lipids, chiefly cholesterol, but also phospholipids¹⁴⁰⁸, into the subendothelial tissue, various factors have been held responsible, e.g., the transportation of cholesterol esters by lipophage cells¹⁹⁴⁵, a precipitation of a cholesterol film on the intimal surface due to a primary disturbance in the plasma colloid equilibrium and resulting in nutritional injury to the vascular wall which in turn would favor the phagocytic absorption of lipids into the subendothelial space¹⁵⁹⁶, a decrease of the cholesterololytic power of the blood⁷¹⁰, an increase of plasma cholesterol concentration per se^{443 215 1914}.

Although there hardly can be any doubt that under certain circumstances hypercholesterolemia will substantially contribute to lipid depositions in the intima, it is no longer believed that this factor is a decisive one^{705 1136 1914 2229 2502 2538}, unless combined with specific peculiarities of the circulating cholesterol itself and of other accompanying plasma constituents. An equimolar relation between free cholesterol and phospholipid in the plasma seems to be necessary to prevent the former from being precipitated^{1615 2541}. Phospholipid to total cholesterol ratios lower than 1.0 were observed with significant frequency in patients with atherosclerosis and coronary thrombosis²²⁴¹. Thus, the amounts of circulating phospholipids^{703 1715}, especially lecithin²⁶²¹, and of certain protein fractions^{2521 2502} influence cholesterol precipitation. Certain lipo-protein compounds of large molecular size (S₁ 12-20 and S₁ 35-100) were found to be related to atherosclerosis and myocardial infarction^{1165 1166}, regardless of total cholesterol levels. The large particles of newly absorbed lipids, appearing in the plasma following fat-rich meals (chylomicrons), have also been considered as contributing to the development of intima lipoidosis²²⁷⁵.

As a rule, calcium deposits in the intima are seen only in atheromatous areas as a secondary development, since the intima -

Arteriosclerosis and Related Vascular Lesions

Definition and General Principles

In consideration of the fact that anatomical lesions of the vascular system frequently constitute the causal background of certain cardiovascular syndromes, we shall first direct our attention toward the problem of arteriosclerosis and its relations to the endocrine system.

Since the term "arteriosclerosis" comprises several rather distinct and partly independent pathological features affecting the arterial system, it seems appropriate to start out with a brief definition of those vascular lesions which are generally included in the collective designation "arteriosclerosis".

The three layers of the arterial wall, intima, media and adventitia, are present in all ramifications of the arterial vascular tree down to the arterioles. However, while the qualitative character of the endothelial intima and of the connective tissue adventitia does not display any major variations throughout the arterial system, there are marked differences in the structure of the media which permit the distinction of three categories of arteries, namely (a) the large elastic arteries whose media layer consists prevalingly of elastic tissue with only sparse admixtures of muscular fibers, (b) the medium-sized muscular arteries with a prevalence of muscular tissue, and (c) the smaller arterioles whose walls are almost entirely composed of smooth muscle cells.

Although the usually rather whimsically and irregularly distributed arteriosclerotic lesions often affect intima and media simultaneously in identical sections of the individual vessels, this cannot be considered a standing rule, as the media may appear entirely intact underneath an area of severe intimal destruction, whereas, on the other hand, a thoroughly degenerated media may be covered by a layer of perfectly normal intimal endothelium. This fact alone suggests a considerable degree of mutual metabolic independence of intima and media and makes the separate occurrence of certain hormone-induced lesions in intima and media intelligible.

In the following, we shall consider those alterations of the intima and media whose at least partial causation by endocrine and neurohormonal interferences is made probable by experimental observations and by their specific occurrence in certain endocrine syndromes.

Lesions of the intima. The most common lesions of the intimal endothe-

tosis through artificial sympathetic stimulation, however, suggests an epinephrine-like morphogenic action of nor-epinephrine. Even more significant are the vascular lesions seen in *pheochromocytoma* cases in which an excessive secretion of nor-epinephrine, paroxysmal or chronic, constitutes usually the outstanding hormonal abnormality (p. 86). They include both atheromatous changes of the large vessels and arteriolar sclerosis, especially of the kidneys. As far as the latter feature is concerned, it seems probable that the constant passage of nor-epinephrine and of its derivatives through the renal vessels in the process of urinary excretion may expose these vessels to the functionally and structurally toxic effects of the catecholamines (p. 15) beyond their tolerance limit.

The total amount of epinephrine in the adrenals of arterio-sclerotic individuals was reported as being about 50 per cent higher than in normals¹¹⁰, but there is little evidence for a significantly exaggerated secretion of epinephrine from the adrenal medulla into the blood circulation in arterio-sclerotic patients, at least judging from the normal blood levels in hypertensive individuals²⁰³².

The exact mode of action by which the adreno-sympathogenic neuro-hormones exert their injurious influence upon the vascular walls is not yet clearly understood, but it can be assumed that both their *mechanical* and *chemical* actions participate. The former are probably composed of an increased hydrostatic pressure upon the vascular cells and of a locally ischemia-producing constriction, plus compression of the vascular musculature and of its vasa vasorum; the chemical mechanism would consist of a direct hypoxia production through excessive oxygen wastage and accumulation of non-oxidized acid metabolites (lactic acid, etc.) in the arterial muscle cells, in analogy to the deleterious hypoxiating metabolic activity of epinephrine and nor-epinephrine, as it has been proven for the heart muscle (p. 11ff). Direct studies of arterial metabolism under the influence of sympathomimetic catecholamines appear as one of the most urgent requirements of arterio-sclerosis research.

Epinephrine is absorbed by arterial tissue *in vitro*³³⁴. The constant presence of epinephrine-like catecholamines in the *regulation* ...

... an increase of the concentration of catecholamines in the aortas (as well as in the kidneys and heart muscle) was noted with a maximum for the aorta in the sixth decade, followed by a slight decline in advanced senescence²⁶¹ (Fig. 25). No definite explanation for these age changes can be offered at the present time except the fact that the lipid content of the aortic wall, including phospholipids, increases with advance-

teristics of the media in different sections of the arterial tree, there exist also differences in the pathological changes occurring in the media of the respective vascular categories. Hyalinization and fibrosis are more conspicuous in the smaller muscular arteries while extensive necroses and calcifications appear with greater frequency in the elastic tissue of the large vessels. Among the pathogenic factors which are supposed to contribute to these lesions, the following have been considered as important¹⁵⁸⁵: abnormally increased or decreased vascular tone; increased intravascular hydrostatic pressure, with compression of the vasa vasorum and over-stretching of both elastic and muscular elements; abnormally decreased hydrostatic pressure (local or general) resulting in a diminished blood supply to the media tissue; constriction of the vasa vasorum; alterations of plasma colloids, leading to film formation and precipitations on the intima. Local hypoxia, to which the smooth muscle cells are particularly susceptible, seems to constitute the common denominator of these conditions due to their interference with the blood flow in the vasa vasorum or with the normal gas exchange between the circulating blood and the tissue of the vascular wall. To these alternatives, a directly hypoxiating chemical effect of neurohormones may be added (p. 11 ff.) as a definite possibility. Calcifications take place in necrotic areas of the media but can also be induced by hypercalcemia per se^{792, 776}, especially under the influence of an acid diet¹⁷⁶⁹. Recently produced experimental and clinical evidence suggests that arteriosclerotic lesions may develop by episodic stages and in "crops" which can be autoptically identified¹⁵⁸⁷.

Inflammatory necrotizing and fibrinoid lesions of the periarteritis nodosa type tend to merge gradually with endarteritic changes, hyalinization of the media and final obliteration, caused by thickening of the intima.

Role of Adrenosympathogenic Neurohormones

Experimental observations (p. 15) have shown that the administration of epinephrine in large doses gives rise to necrotic calcifying lesions of the media of the larger vessels, while prolonged series of smaller dosed injections produce also thickening of the intima and involvement of small arteries. The formation of cholesterol atheromatosis is markedly intensified and hastened by epinephrine, probably due to direct primary injury of the intima. No data on the effect of experimentally administered nor-epinephrine upon vascular structural integrity are yet available, although studies regarding this question would be particularly interesting in view of the fact that nor-epinephrine, as the physiological product of direct sympathetic neurosecretion into the cells of the arterial walls³⁰¹⁷, is probably far more important for the origin of the common forms of arteriosclerosis than epinephrine. The observation of an intensification of cholesterol atheroma-

ficial electrical sympathetic stimulation¹⁹⁰⁸ and by observations concerning the limitation of arteriosclerotic changes to extremities which had performed strenuous work over longer periods of time^{1904, 1902}. An asymmetrical development of arteriosclerotic lesions in both radial arteries was seen according to right- or left-handedness¹⁷⁰⁷, and a significantly higher incidence of arteriosclerosis of the legs was reported in stair-climbers as compared



FIG. 26
of atherosclerosis

with non-stair-climbers.¹⁹⁰⁴ The markedly accentuated intensification of coronary sclerosis and myocardial infarctions in animals which had been forced to run in a treadmill^{1902, 1903} belongs probably in the same category of largely neurogenic vascular lesions.

It seems a conceivable possibility that such lesions might be enhanced by simultaneous adrenal mineralocorticoid action and by its influence upon intracellular electrolyte distribution (p. 23). In that case, the stimulating effect of circulating epinephrine upon the liberation of corticotrophic hormone from the anterior pituitary lobe and thus upon adrenal cortical secre-

ing years^{401, 437, 2231, 2531}, that epinephrine and nor-epinephrine possess a specific affinity to lecithin with which they form compounds which are soluble in organic solvents^{1716, 2149, 2675}, and that lecithin penetrates even easier than cholesterol into the tissue of the larger vessels²⁶²². The presence of relatively large quantities of phospholipids in the adrenal medulla has been pointed out as possible indication of a compound formation with epinephrine¹⁸⁷². Alcoholic extracts of serum lipids, made by the writer from the blood of hypertensive and arteriosclerotic individuals, acted like epinephrine-containing lipid compounds, obtained from the adrenals, in enhancing the formation of intima-lipoidosis in cholesterol-fed rabbits²⁶⁶⁴ (Fig. 26)

The concentration of epinephrine-like catecholamines in arteriosclerotic

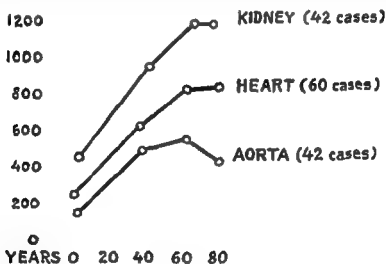


FIG. 25 Increase of catecholamine concentration in tissues with advancing age (color units per gram)

(After W. Raab, Arch. Path. 35: 836, 1943)

human aortas, renal arteries and kidneys was not found significantly higher than in normal specimens²⁶⁷², but this does not exclude the possibility that high concentrations might have existed at an earlier stage, years before the autopsy when the vascular lesions were established, nor does it rule out a possible functional potentiation of these amines through adrenal cortical steroids as it has been shown regarding the pressor action of both epinephrine and nor-epinephrine^{2098, 2704, 2913}.

Whether or not degenerative changes which were observed in the sympathetic ganglia furnishing the innervation of arteriosclerotic vascular areas^{2222, 3367} are to be interpreted as residues of an earlier state of abnormal irritation and over-activity, cannot be decided at this time. Exaggerated local sympathetic neurosecretion seems to contribute to the development of regional arteriosclerotic lesions. This is suggested by experiments with arti-

likely that the nicotine-induced vascular changes are ultimately caused by an increased secretory activity of the adrenal medulla, and perhaps even more so by discharges of nor-epinephrine from post-ganglionic sympathetic fibers directly into the cells of the vascular wall tissue. The blood level of epinephrine-like catecholamines in heavy smokers²⁶² and during acute intense tobacco smoking²⁶¹ did not show any striking changes, but a slight upward tendency was noticeable.

Insofar as an *increased vascular tone and hypertension* are believed to contribute to the development of arteriosclerotic lesions by interfering with the blood flow through the vasa vasorum and by exerting an abnormal hydrostatic pressure upon the arterial wall cells¹⁴⁸, the apparent participation of the adrenosympathetic neurohormones in the pathogenic mechanism of essential hypertension (p. 263) might be considered as another mode of action by which these catecholamines may serve as arteriosclerogenic agents. Atheromatosis of the larger vessels, although present in some patients with essential hypertension, is not a characteristic feature of this disease^{149, 210} and is also frequently found in non-hypertensive individuals. Arteriolar sclerosis of the smaller muscular vessels on the other hand has been reported as existing in 90-97 per cent of several large series of cases of essential hypertension^{148, 278} and is regarded as its typical morphological vascular substrate. However, arteriolar sclerotic lesions are occasionally encountered also in non-hypertensive persons²⁷⁹. A certain percentage of hypertensives is free of such changes, and the distribution of the latter within the arterial tree differs considerably from person to person. These facts cast some doubt on the validity of the assumption that the mechanical hypertensive state per se constitutes a very important factor in the origin of arteriolar sclerosis.

The interpretation of Evelyn²²⁹, who considers arteriolar sclerosis and essential hypertension as primarily independent processes, is a basically sound one, but this mutual "independence" seems to concern their occurrence rather than their causal background. There remains the probability that a chemical interference of the locally discharged sympathetic neurohormones in the muscular tissue metabolism of varying sections of the arterial system might be the cause of both functional (constrictor) and morphogenic (sclerosing) reactions, the simultaneous presence of

the development of arteriolar sclerosis in nephrectomized dogs which were kept alive by peritoneal lavage¹²⁹⁴ suggests the possible causal role of substances retained in the system.

tion, might constitute an additional indirect factor in the mechanism of neurohormone-induced vascular damage.

Psychic mechanisms, which are capable of provoking adrenosympathetic secretion, have been considered as contributing to the development of arteriosclerosis, especially of the coronary arteries. Several statistical reviews^{117, 1203, 1434, 2318, 2350, 2163} seem to make it probable that intellectual occupational groups and businessmen are far more frequently afflicted with coronary disease in particular than manual laborers. For instance, according to one statistical study²¹⁶³, the incidence of coronary sclerosis within the medical profession group was 10.7 per cent, within the banking group 5.3 per cent, within the ministerial and legal group 4.6 per cent and within the labor and agricultural groups 2.5-2.6 per cent. An early development of cerebral arteriosclerosis was likewise claimed to occur among persons living under emotional stress^{542, 205}. Apart from the fact that the above-mentioned statistical data have not remained uncontradicted^{2000, 2255}, it appears doubtful that psychic tensions and emotional conflicts alone should account for such marked differences between the social strata. Emotional intensity and instability, frustrations and hostilities are not privileges of the white-collar workers and the strictly intellectual part of their mental functions is not likely to stimulate the adrenal medulla excessively. It appears more probable that physical living habits play a major role in the pathogenesis of arteriosclerotic lesions, especially of the heart. This can be concluded from the fact that the signs of coronary sclerosis are remarkably uncommon among trained sportsmen with a prevalence of vagal tone²¹⁶⁹. The vagus antagonizes the oxygen-wasting effects of sympathetic neurosecretion in the heart muscle^{1195, 1199a, 1269}, keeps the blood pressure on a lower level and thus appears to be well suited to protect the cardiovascular system from the injurious hypoxia-producing influence of uncontrolled sympathetic neurosecretory activity. Physically untrained people, whether intellectual or not, are handicapped by a deficiency of vagal counterbalance against their pampered, unruly adrenosympathetic system.

There exists a well established causal relationship between a frequent occurrence of vascular damage¹⁵⁹⁶, especially of thromboangitis obliterans, coronary sclerosis^{573, 2669}, cerebral arteriosclerosis¹²⁰³, and peripheral arteriosclerosis²³³² on the one hand, and the introduction of *nicotine* into the body by smoking or industrial occupation with tobacco on the other. It can be considered as further indirect proof of the role of adrenosympathetic neurosecretion in the pathogenesis of arteriosclerotic lesions. Nicotine stimulates the sympathetic system at the ganglionic synapses and mobilizes epinephrine from the adrenal medulla^{466, 844, 2151, 2223, 2275}. Its experimentally produced destructive effects on the vascular walls of animals are identical with those elicited by epinephrine injections^{1596, 1824, 2191}. Hence, it appears most

likely that the nicotine-induced vascular changes are ultimately caused by an increased secretory activity of the adrenal medulla, and perhaps even more so by discharges of nor-epinephrine from post-ganglionic sympathetic fibers directly into the cells of the vascular wall tissue. The blood level of epinephrine-like catecholamines in heavy smokers²⁹² and during acute intense tobacco smoking²⁹³ did not show any striking changes, but a slight upward tendency was noticeable.

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the development of arteriolar sclerosis in nephrectomized dogs which were kept alive by peritoneal lavage¹⁷⁹ suggests the possible causal role of substances retained in the circulation.

A specific form of severe general vascular damage, designated as *necrotizing arteriolitis*, constitutes a frequent disastrous complication of the

malignant type of essential hypertension and of acute or chronic glomerulonephritis with renal excretory failure¹⁵⁹⁶. It could be experimentally duplicated by renal arterial constriction of a degree which caused a definite excretory insufficiency of the kidneys¹⁷⁷², and has been ascribed to the accumulation of some unknown "metabolites" in the blood¹⁵⁹⁵. The vascular lesions consist of a marked proliferation of the intima with fibrinoid deposits, necroses of the media and leukocytic infiltrations of the adventitia, resembling those seen in periarteritis nodosa¹⁵⁹⁶. Similar extensive and rapidly developing necrotizing arterial and arteriolar lesions were produced in dogs, fed on a high fat diet, by the establishment of renal excretory insufficiency through nephrectomy or kidney damage¹⁵⁵³ and in pregnant animals by constriction of the kidneys or renal arteries^{693, 747}. Although it appears obvious from experimental and clinical observations that renal excretory failure is an essential prerequisite for the form of arterial disease in question, a widespread necrotizing arteriolitis has been observed in cases of pheochromocytoma also in the absence of definite renal insufficiency³⁵⁰⁹.

This apparent contradiction can perhaps be explained by considering one feature which cases of pheochromocytoma and of renal failure have in common, namely the presence of excessive amounts of catecholamines of adrenosympathetic origin in the blood. In the first case, this is due to the secretory activity of the tumor, in the latter case, to insufficient renal excretion of catecholamines. Excessive quantities of catecholamines were regularly obtained from the blood and heart muscle of uremic patients³⁶⁷⁶. This will be discussed in greater detail on p. 478. No data are yet available which would permit any definite conclusion regarding an actual involvement of these substances in the origin of necrotizing arteriolar lesions in patients with renal failure, but their regular presence in the uremic blood seems to be of interest for the evaluation of the problematic necrotizing "metabolites".

Whether the therapeutic results of sympathectomy in cases of peripheral vascular disease (lit., see⁶⁹³) are due exclusively to the relaxation of vascular spasms and opening up of collaterals or also to a certain amount of structural repair of damaged vessels, is difficult to decide. However, the retardation or entire prevention of the progress of peripheral vascular lesions by sympathectomy emphasizes the important role of local sympathetic neurosecretion in the pathogenic mechanism of these types of vascular disease.

Role of the Adrenal Cortex

Experimental implantation of adrenal tissue and administration of mineralocorticoids, such as *DCA* and *17-hydroxy-11-desoxycorticosterone*, can produce endarteritis- and periarteritis-like arteriolar lesions. The develop-

ment of atheromatosis of the larger vessels is neither significantly enhanced by cortical extracts nor prevented by adrenalectomy (p. 32). On the other hand, there exists a striking analogy between the often severe and generalized atheromatosis and arteriolar sclerosis which occur in the majority of patients with hyperadrenocorticism (Cushing's syndrome), even in children (p. 98 ff.), and the common forms of arteriosclerosis in which a pathogenic involvement of the adrenal cortex is not so conspicuous. Most statements in defense of a prominent adrenocortical factor in the origin of ordinary arteriosclerosis refer to these analogies^{149, 150, 264}, but there is only scant direct evidence on hand despite the undeniable probability of such relations.

An increase in size of the adrenal cortex has been repeatedly claimed to be a characteristic of arteriosclerotic individuals^{60, 119}. Such enlargements and small cortical adenomas are also often present in hypertensive persons and have been held responsible for both the high blood pressure and co-existing arteriosclerosis (p. 233). However, apart from the fact that an enlargement of the cortex per se does not necessarily prove an excessive secretory activity, there is considerable dissension of opinions regarding the regularity and specificity of such findings^{267, 111}. Greater importance may perhaps be attributable to the cholesterol content of the cortex which has been found characteristically elevated in arteriosclerotic (lit., see ²⁶⁷) and hypertensive individuals^{291, 190, 172, 277}, while the phospholipids of the adrenals are reported to be diminished in hypertensives¹⁷², supposedly because of increased secretory elimination.

In view of the tendency of catecholamines to form compounds with lecithin^{174, 216, 261}, it seems possible that epinephrine, entering the blood stream with a

the observation of an exceptionally high concentration of epinephrine-like catecholamines in the walls of the aorta and renal artery of a patient with a small cortical adenoma²⁷⁷, suggests likewise some relationship between cortical and adrenosympathetic hormone production. Whether the augmentation of the pressor effects of epinephrine and nor-epinephrine by DCA^{2096, 2101, 2791, 2912}, which seems to be mediated by intracellular sodium deposition²⁸⁹, contributes also in some way to the development of arteriosclerosis, cannot be evaluated at this time. Certainly, the functional relations between adrenal cortex and medulla deserve more attention than they have received up to the present.

As far as the role of cholesterol in the origin of arteriosclerosis is concerned, general interest is being focused on the fact that it serves as the "raw material" for the development of atheromatosis in the arterial intima (p. 245), but it must be ably also represents

From this point of view, the chronic excessive ingestion of cholesterol would appear as a possible antecedent to increased corticoid elaboration, and the question of the significance of a high fat and high cholesterol diet in the pathogenesis of arteriosclerosis must be considered also in this respect.

In 1932, the writer²⁶³ carried out a world-wide inquiry for information from individual investigators, hospitals, insurance agencies, medical missionaries, etc., regarding the occurrence of arteriosclerosis and its clinical manifestations among various nations, racial, social and religious groups, in relation to their dietary habits. Although only few statistically tangible data were obtained, a survey of all the answers received gave the definite impression that arteriosclerosis is less common among people whose diet contains a minimum of animal fat, egg yolk, and dairy products, as compared with those consuming large quantities of foodstuffs rich in lipids and cholesterol. Similar conclusions were drawn by Leary¹⁹⁴, Snapper²¹⁶, Steiner²²⁰, and others, but the question cannot be considered as settled as long as no world-wide, exact statistical studies with due consideration of various other possibly interfering factors have been organized.

There does not exist any clear-cut relationship between the dietary intake of cholesterol within certain limits and the blood cholesterol level^{131, 209}, as the latter is largely dependent on cholesterol synthesis and utilization within the body itself besides the alimentary ingestion¹³¹. Statements regarding a direct relation between the cholesterol content of the diet, the blood cholesterol level²²⁸, and the incidence of coronary sclerosis^{254, 261, 262} have been challenged^{1131, 2099}. Thus, some basic problems of the role of cholesterol in the development of arteriosclerosis must still be considered as unsolved, but despite the apparent inconsistencies of many details, there can hardly be any doubt that cholesterol and other lipids are in some yet obscure way profoundly involved in the origin of arteriosclerosis and of its endocrine background. The relations between familial hypercholesterolemia, xanthomatosis and arteriosclerosis point in the same direction^{12, 214, 220}. Racial factors may be of significance but are only inadequately explored¹³⁹⁴. The incidence of advanced atherosclerosis was found about twice as high in obese individuals at autopsy as in a comparable large series of poorly nourished persons²⁶²¹.

Selye's interpretation of arteriosclerosis as a phenomenon, pertaining to the "general adaptation syndrome"²³⁰⁷ and representing the end result of a lifetime of pituitocortical "alarm reactions", is still in need of confirmation in many respects. However its fundamental concept is not only impressive as a stroke of intuitive genius, but it appears also so well suited to explain the writer wishes to stress as a heretofore insufficiently emphasized but

nevertheless vitally important complement to the adrenocortical mechanisms of the adaptation syndrome, is the apparently intimate mutual functional correlation between adrenosympathetic catecholamines and adrenal corticoids. There are numerous reasons to consider the former as the more immediately toxic agents, especially under the potentiating influence of the adrenal corticoids, while the mobilization of the latter into action is largely initiated by these very neurohormones whose effectiveness they seem to intensify.

Role of the Thyroid

Despite its epinephrine-activating effect and although it enhances the injurious influences of desoxycorticosterone upon the arterial walls, there exists experimental evidence (p. 38) for one specific vasculotropic action of the thyroid hormone which contrasts sharply with that of the adrenal hormones in that it entails a *protection of the arterial intima against lipid deposits*. Only very large doses of thyroid hormone, which have no parallel in human pathology, seem to tip the balance between its two competing tendencies toward the development of epinephrine-like vascular lesions, and give rise to nephrosclerotic changes. Clinical vascular conditions in hyperthyroidism and hypothyroidism (pp. 140 and 156) are in agreement with experimental observations in that arteriosclerotic changes are not prominent in thyrotoxic cases, while hypothyroidism is frequently associated with premature and severe atherosclerosis. Arteriolar sclerotic changes do not seem to be provoked by either hyper- or hypothyroidism.

There is only little that can be said about the actual role of the thyroid gland in the natural history of *arteriosclerosis*.¹⁰ There is no conclusive statistical data yet.

¹⁰ *On the structure and function of the thyroid gland*. According to post-mortem studies, both the total size and the size of the follicles of the thyroid are diminished in older individuals. The intensity of the changes increases with age. The authors conclude that the thyroid gland atrophies with age. A

¹¹ *On the structure and function of the thyroid gland*. Specifically concerning the problem of arteriosclerosis, it was stated by Bruger and Rosengerant¹¹ that arteriosclerotic persons above the age of 55 years had a significantly lower basal metabolism than a comparable group of non-arteriosclerotic individuals. The authors arrive at the tentative conclusion that "it is conceivable that the receptivity of the vascular tree to the deposition of lipids may vary inversely with the activity of the thyroid gland," but they consider also other possibilities, e.g., that the reported thyroid atrophy in arterio-

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garding the functional significance of the different cell elements of the anterior lobe has been further heightened by the claim that the adrenotrophic action, heretofore ascribed to the basophils, be inherent in the eosinophils instead, and attenuated by degeneration of the basophils^{111, 112, 113}. From the point of view of this concept, various disorders of old age were interpreted as being caused by a hypothetical relative over-activity of the eosinophils, due to a hypothetical underfunction of the basophils, due to a hypothetical under-function of the neurohypophysis, due to a hypothetical under-function of the hypothalamus¹¹⁴.

Another controversial problem is the significance of the invasion of the posterior pituitary lobe by basophil cells in arteriosclerotic and hypertensive individuals to which Cushing had called attention⁶⁴. The phenomenon in question was subsequently observed to occur also in persons without vascular disease and to be absent in a number of those in whom it had been expected (ibid., see ¹¹⁵). The late Dr. Cushing himself expressed doubts in his own preliminary conclusions in a letter to the writer in 1934, as follows: "I do not want you to take this hypothesis of mine concerning posterior lobe basophilia too seriously, for I have only thrown it out . . . with the idea of getting the pathologists to examine the pituitary body more frequently and at the same time more methodically." Several reports seem to justify a denial of any major role of the posterior pituitary lobe in the origin of arteriosclerosis¹¹⁶.

Observations of *pituitary hormone production and excretion*, which would have some bearing on the problem of arteriosclerosis, are scarce and of limited informative value. Reports on the eosinopenic response to epinephrine in old age are conflicting^{117, 118}. The ability of the adrenal cortex to discharge 11-17-oxysteroids¹¹⁹ and 17-ketosteroids¹²⁰ under the influence of injected ACTH was not found to be noticeably altered, even though fibrosis and a decrease of epithelial cells seem to be a characteristic of the senile adrenal cortex¹²¹. The latter is said to be generally enlarged rather than decreased in size^{122, 123}. A reduced secretion of thyrotropic hormone in aged individuals¹²⁴ may be regarded as a corollary of the low basal metabolic rates mentioned on p. 255. The typically low urinary excretion of 17-ketosteroids by senile persons of both sexes^{125, 126, 127, 128, 129} is to be attributed to a diminished steroid production of the adrenal cortex and the gonads in the male and of the adrenal cortex alone in the female¹³⁰, possibly resulting from a decreased output of adrenotrophic hormone from the hypothalamus.

In summary, the evidence for

the role of anterior pituitary function in the pathogenesis of atherosclerosis and arteriolar sclerosis, probably by means

sclerotic persons might be a sequel rather than a cause of vascular lesions. It has been pointed out^{1709, 2226b} that it may not be the calorogenic effect of the thyroid hormone which is responsible for its influence upon vascular structure. In this connection, it should be remembered that the basal metabolism is not entirely dependent on the thyroid hormone but largely determined by adrenergic catecholamine action so that a low basal metabolism does not necessarily prove thyroid hypoactivity.

Role of the Pituitary

In view of the multiplicity of pituitary hormones and their interplay, it is not yet possible to ascribe vascular lesions which seem to be related to pituitary function to any single one of these hormones. The results of experimental administration of crude anterior lobe extracts (p. 48) resemble those of DCA to such a degree that the assumption of secondary adrenal cortical activation appears probable. The effects of purified ACTH are less impressive for unknown reasons. The marked tendency toward the development of atherosclerosis and arteriolar sclerosis in cases with Cushing's disease and acromegaly (the latter apparently with less arteriolar involvement) (pp. 98 and 167) and the absence or scarcity of such vascular lesions in hypopituitarism, agree in principle with the experimental observations, however, without contributing any precise information regarding the types of pituitary and adrenal hormones which may participate in the origin of common arteriosclerosis.

Inasmuch as arteriosclerosis is considered a disease predominantly of old age, attempts were made to correlate morphological changes of the pituitary, appearing in senescence, with the pathogenesis of arteriosclerosis. Because of their suspected role in Cushing's disease, special attention was paid to the *basophil cells of the anterior lobe* and to their numerical proportion to the eosinophil cells. The total weight of the pituitary gland was reported as decreasing after the 50th year^{2711, 2720} and the number of eosinophil cells as diminishing^{2542, 2711, 3662}, while the basophil cells were described as augmented^{2712, 2714}. An increase of basophil cells was claimed to be present with particular frequency, although by no means regularly, in patients with nephrosclerosis and chronic nephritis^{2720, 1322, 1522, 2122} and with arteriosclerosis in general²⁵⁹².

It was pointed out by the writer many years ago²⁶⁶⁰ that certain similarities of Cushing's syndrome with some features of old age (arteriosclerosis, hypertension, sexual regression, osteoporosis, fat distribution, atrophy of the skin) suggest a specific significance of the basophil cells for the process of aging, but today the functional position of these cells in the endocrine system appears much more problematic than originally. The confusion re-

upon cardiovascular tissue, which constantly threatens its anatomical and functional integrity (p 11, 15, 18).

Role of the Parathyroids

Ever since it was observed that the experimental administration of large doses of parathyroid hormone produces marked, diffuse, necrotic lesions and calcification of arterial walls (p. 58), the question has been raised as to whether parathyroid secretory activity might in some way contribute to the pathogenesis of arteriosclerosis, but nothing definite can be said as long as no technical means for the direct measurement of parathormone secretion are available. A reported increase of the number of oxyphil cells in the parathyroid glands of arteriosclerotic individuals⁶⁹ may or may not be of significance. Data on the presence and characteristics of vascular lesions in patients with primary hyperparathyroidism are too scarce for a critical comparison with ordinary arteriosclerosis, and the vascular lesions seen in cases of secondary parathyroid hyperfunction, induced by primary kidney disease (lit., see¹⁵⁰) cannot be interpreted as directly resulting from parathyroid hormone interference. Thus, the problem of parathyroid involvement in the pathogenesis of arteriosclerosis must be considered as entirely unsettled and as actually inaccessible pending the development of adequate new methods for the study of unequivocal criteria.

Treatment

The wording "treatment of arteriosclerosis" appears almost a contradiction in adjecto in view of the generally recognized impossibility to induce a regression of established arteriosclerotic vascular changes, except perhaps by diet, which, like methionine and niacin, is effective, at least in animals⁶¹, and by cholesterol-lowering agents, which, like methionine and niacin, possess certain decholesterizing properties¹⁰³. Wykoff's statement²⁴⁹ in 1933: "At present, the only effective mode of therapy is the removal of the atherosclerotic material from the midst of the artery" is still valid. The only therapy

Our discussion of therapeutic measures to be taken in arteriosclerotic patients will, therefore, have to be confined to the alleviation of complicating symptomatic cardiovascular features, as in angina pectoris (p. 388 ff.), congestive heart failure (p. 507 ff.), nephrosclerosis (p. 317 ff.), etc.

Peripheral vascular disease has been attacked with gratifying success by reduction of locally constricting sympathetic neurosecretory discharges through (preferably bilateral) lumbar sympathectomy, which can be considered the method of choice²⁵ 154 560 691 729 1126, 1268, 2266, 2361, 2422, 2545 also

of its various glandotrophic activities, there is a paucity of conclusive data which would permit any positive evaluation of the specific pituitary functions participating.

Role of the Gonads

A similar uncertainty concerning details of action prevails in regard to the role of the gonads in the origin of arteriosclerosis. Experimental observations (p. 56) revealed some protective power of gonadal steroids against the formation of cholesterol atheromatosis, as well as an accentuation of the latter and of the DCA-induced arteriolar lesions following gonadectomy. Certain alterations of the protein composition of the arteriolar walls seem to be involved in these reactions. In young men with coronary sclerosis, the urinary excretion of 17-ketosteroids was not found abnormal¹¹³.

A causal connection between the progress of arteriosclerosis in the later stages of life and its partial coincidence with the period of sexual involution has long been suspected, but here again we have to be contented with impressions for the time being, since the specific data available, of which a few are mentioned on p. 56 ff., do not contribute substantially to a clearer understanding of the part which the gonads and their interaction with the pituitary and the adrenal cortex play in the pathogenesis of arteriosclerosis.

Role of the Pancreas

There do not exist any experimental observations which would suggest a direct action of insulin, injurious or protective, upon the vascular system (p. 52).

The specificity of a few instances of arteriosclerosis of the aorta and the coronary arteries in pancreatectomized animals has not been proven. Neither can the well-known aggravation of general arteriosclerosis, coronary sclerosis, peripheral vascular sclerosis and intercapillary glomerular sclerosis (Kimmelstiel-Wilson) of diabetic individuals (p. 214) be attributed simply to an insulin deficiency. Pituitary and adrenal cortical functional disturbances of a still unclarified nature are believed to form the endocrine background of the diabetic metabolic derangement. Even in those cases in which a primary pancreatic lesion can be suspected, one may have to reckon with a secondary imbalance of other endocrine glands, resulting from the abnormal carbohydrate metabolism and possibly enhancing the progress of arteriosclerosis. Hence, it appears unlikely that the physiological variations of insulin secretion in non-diabetic persons should exert any significant influence upon the structural state of the vascular system. It is possible, however, that the secondary moderate epinephrine discharges following postprandial insulin-induced hypoglycemic episodes¹¹⁴, might participate in the life-long series of hypoxiating attacks of the adrenosympathetic system

in the origin of arteriolar sclerosis. Their mode of action on the vascular walls is still unknown. There is some reason to suspect a cooperation with the adrenal medullary and sympathogenic catecholamines.

The intimal lipid deposition is specifically enhanced by a deficiency of thyroid function (partly due to the accompanying hypercholesterolemia) and counter-acted by the thyroid hormone and the gonadal steroids. Hemodynamic and hydrostatic mechanisms under neuroendocrine and hormonal control seem to elicit additional sclerosing effects on the arterial walls through interference with the blood flow within the vasa vasorum, etc. A possible role of the parathyroid hormone in the process of calcification of vascular lesions remains to be proven. Detailed statistical analyses of the neurosecretory and endocrine functional patterns in arterio-sclerotic persons should help to answer various as yet unsolved questions of the arterio-sclerosis problem.

Only few theoretically rational preventive measures, such as avoidance of excessive sympathetic neurosecretory stimuli, of excess lipids in the diet, of tobacco smoking etc., are practically feasible. An effective therapy which would promise regression of established arterio-sclerotic lesions does not exist. The progression of peripheral arterial disease can be retarded by sympathectomy or medicinal interference with the local activity of neurogenic catecholamines. The treatment of various cardiovascular complications which are caused by arterio-sclerosis will be dealt with in the following sections.

for patients beyond the 70th year and even in the presence of frank gangrene. Formerly unattainable improvements of the peripheral circulation are now possible. Preservation of the diseased extremity could be achieved by sympathectomy in 35 per cent of one large series of cases of gangrene⁶⁹. The only counter-indications are advanced lesions of other vital organs, marked atrophy of the limb and severe ischemic neuritis with intractable pain which cannot be relieved by sympathectomy⁶⁹. As regards the differentiation between cases offering a better or poorer outlook for surgical intervention, the response to temporary sympathetic block proved a less reliable criterion than used to be believed⁶⁹ so that patients showing no immediate favorable reaction must not necessarily be considered unsuitable for the operation.

Non-surgical measures, such as the use of sympatholytic agents, e.g., priscoline^{1032, 1164, 1237, 2050a, 2935, 3019} or dihydrogenated ergot alkaloids^{1701, 2524}, tetraethylammonium (TEA)²¹¹⁴, and X-ray irradiation of the adrena and lumbar area^{712, 1147, 1517, 1916, 2663, 3709}, have been applied with satisfactory results in a fair percentage of cases, but can hardly compete in effectiveness with the surgical procedures, especially in advanced stages. They have a place, however, in the milder forms of peripheral vascular disease and may be combined with the administration of sexual steroids^{839, 1523, 2143, 2155, 2162} even though the value of the latter has been questioned³⁷²².

Summary

Many impressive similarities exist between the atheromatous and arteriolar sclerotic lesions characteristically occurring in such endocrine syndromes as hyperadrenocorticism, pheochromocytoma, acromegaly, diabetes, and myxedema on one hand, and the common forms of arteriosclerosis on the other. This fact, as well as the possibility of inducing arteriosclerotic changes by corresponding experimental interferences in the endocrine system, and the conspicuous scarcity of arteriosclerosis in hypoadrenocorticism and hypopituitarism, make it practically certain that the development of arteriosclerosis in general is essentially caused by endocrine factors.

The experimentally (on the heart muscle) well established specific, locally hypoxiating metabolic action of sympathomimetic catecholamines, which are directly discharged from sympathetic fibers into the vascular wall tissue, can be suspected as being largely responsible for degenerative and necrotic lesions of the muscular elements in the media of the smaller arteries. Besides, an exaggerated activity of catecholamines seems to alter the arterial intima in such a fashion that the deposition of circulating cholesterol and other lipids is greatly facilitated.

Adrenal corticoids, probably deriving from cholesterol, and secreted under pituitary adrenocorticotrophic stimulation, seem to play an important part

symptom of hypertension. It is to be hoped that with improving techniques for the practical pathogenic analysis of each individual case, some more descriptive designations will be introduced in due time to replace the discredited term "essential" so that the different factors involved and their relative prevalence in each instance can be adequately emphasized.

For the time being, however, we shall continue to employ the term "essential" for those forms of either labile or fixed arterial hypertension with an elevated diastolic pressure which cannot be attributed to certain clearly defined conditions, such as primary renal disease (polycystic, obstructive, bacterial, glomerulonephritic, etc.), cerebral disorders (encephalitis, trauma, concussion), arteriosclerosis of the larger vessels, coarctation of the aorta, and gross endocrine pathology, such as pheochromocytoma, Cushing's syndrome and toxemia of pregnancy.

In view of the neuroendocrine nature of sympathetic function and its intimate interrelations with the glandular endocrine system, the neurogenic mechanisms of hypertension will be included in the following discussion.

Role of the Adrenosympathogenic Neurohormones ("Neurogenic Hypertension")

For an exact evaluation of the degree of participation of sympathomimetic neurohormonal mechanisms in a given case of hypertension, it would be important (a) to know the quantity of sympathogenic pressor catecholamines present in the arterial walls and (b) the nature and effectiveness of co-existing factors which might modify the contractile response of the vascular cells to the neurohormonal stimulus. Neither of these two postulates can be fulfilled with available clinical methods. However, indirect evidence is to be obtained (a) from estimation of sympathetic cardiovascular tonicity and (b) from criteria of adrenal cortical function which seems to be largely responsible for the vascular dynamic reactions to the sympathomimetic catecholamines (p. 23 ff).

In the following we shall enumerate first of all the reasons for the widespread assumption that an increased sympathetic cardiovascular tone and reactivity constitute the outstanding features in the so-called neurogenic forms of essential hypertension:

- (1) Lability and wide range of variability of the blood pressure,
- (2) Depressor effect of sympatholytic drugs and of sympathectomy;
- (3) Increased pressor effect of peripheral sensory and pain stimuli;
- (4) Increased local vasoconstrictor effect of peripheral stimuli;
- (5) Increased pressor effect of central vasomotor stimuli, such as inhalation of CO₂ and breath-holding,
- (6) Increased depressor effect of centrally inhibitory measures: hyperventilation, barbiturates,

"Essential" Hypertension

Definition and General Principles

The term "essential" hypertension, originally coined by Hensen in 1900¹⁴⁸ to distinguish asymptomatic forms of hypertension from those with manifest cardiovascular complications, was later¹⁰³¹ used in reference to the lack of a recognizable pathogenic factor rather than of symptoms. Thus, by the suggestive power of one adjective, the stage was set for decades of investigative effort under the erroneous presumption that the particular type of hypertension, called "essential", is caused by one single, though unknown, pathogenic mechanism, and different groups of workers proceeded in different directions, each considering its own the only one which would promise a solution of the problem. Devious as these attitudes proved in the end, they nevertheless endowed their champions with that amount of unintentionally biased enthusiasm, spirit of competition and endurance which is necessary to conquer the obstacles blocking the way toward even isolated fragments of the truth.

European investigators concentrated their attention primarily either on renal pathology^{2232, 2442, 2473} or on central nervous mechanisms^{418, 1690}, conducive to hypertension, until interest in pituitary-adrenal dysfunction^{169, 1551} came into prominence under the stimulus of Harvey Cushing's work. In the United States and South America, the experimental production of sustained renal hypertension by Goldblatt (1934)¹¹⁷⁴ was followed by such an exclusive infatuation with purely renal aspects of the problem that for several years it was almost incompatible with good manners to even mention the nervous and endocrine systems among hypertension workers. Despite or perhaps because of such a temporary one-sidedness in the evaluation of the hypertension-producing role of the kidneys, this dramatic period of hypertension research proved extremely fruitful regarding the revelation of facts as well as the stimulation of ideas.

A large portion of the up-to-date accumulated mass of information was admirably coordinated and presented by Schroeder³⁰¹⁰ with perhaps somewhat more emphasis on psychosomatic pathogenic factors than would appear necessary to the writer. In contrast to earlier classifications of hypertension which were largely based on a grouping of various clinical morbid entities, accompanied by an elevation of blood pressure^{2501, 3532}, Schroeder's review³⁰¹⁰ attempts to integrate the more recently recognized or suspected basic mechanisms into the varying pathogenic patterns which occur either independently or overlap, all resulting in the same common unspecific

the carotid sinus itself was usually followed by normal or even exaggerated vasodepression^{12,17,19,21,22,23,24,25}. Results of occluding pressure upon the carotid arteries below the sinus in hypertensive patients were contradictory^{17,19,22,23,25}, but bilateral novocaine blockade of the carotid sinus nerves was regularly followed by an extreme increase of systolic and diastolic pressure and heart rate in various types of clinical hypertension^{19,21} (Table 12). These experiments prove the functional integrity of the depressor nerves of the carotid sinus. However, they leave the question unanswered as to why the vagal depressor reflex mechanism of the carotid pressoreceptors fails to normalize the elevated pressure level of individuals with neurogenic hypertension. It has been claimed that a sclerotic hardening of the intima within the carotid sinus prevents the hydrostatic pressure of the blood from acting upon the adventitial pressoreceptive nerve fibers, while digital pressure from outside would remain fully effective by pressing these fibers against the abnormally resistant underlying tissue^{21,22}. This interpretation has to be modified in the light of more recent findings^{14,15} which prove convincingly that it is not the direct hydrostatic pressure per se which serves as the adequate stimulus for the depressor reflex but the distention of the carotid sinus wall. Volhard's last theory of neurogenic hypertension^{14,15} maintains that a decreasing distensibility of the aging wall of the carotid sinus interferes with the depressor vagal response of the sinus reflex, thus elevating its threshold to ultimate near-non-responsiveness and leaving the

pressor sympathetic system intact. A post-mortem study of the actual state of distensibility of the sinus walls of neurogenic hypertensive and normotensive subjects of comparable age groups. The fact that in hypertensive individuals the sympathogenic pressor responses to blockade of the sinus nerves exceeded those of the normotensives (Table 12), was interpreted as indicating an insufficient counter-regulation from other pressoreceptor vascular areas, presumably for the same reason of diminished distensibility of the arterial walls^{19,20}. It is interesting to note that temporary systolic and diastolic hypertension with tachycardia was observed by Lampen^{19,20} in 10 cases of polyneuritis. It disappeared again with recovery of the patients and was considered as being due to a neuritic involvement of the depressor nerves.

According to a personal communication from the late Dr. J. H. Green, few cases of polyneuritis have been reported in which the depressor nerves were involved.

It has been described as the

sympathomimetic transmitters, participating in the carotid

- (7) Increased depressor effect of spinal anesthesia;
- (8) Apparent inequality of regional vasoconstriction throughout the arterial system;
- (9) Analogies with the hemodynamics of pheochromocytoma-induced sustained hypertension and with the hemodynamic effects of infused norepinephrine;
- (10) Frequent elevation of the basal metabolic rate in apparent analogy to the calorogenic effects of the sympathomimetic catecholamines.

Finally, there may be mentioned the parallelism between the cardiac, renal, and ocular complications of pheochromocytoma and the practically identical features, characterizing the advanced stages of "essential" hypertension.

As far as the origin of abnormal stimulation of sympathetic neurosecretory activity is concerned, one has to consider several different sections of the reflex arch in which such changes can take place:

- (1) Any peripheral tissue elements connected with the vasoconstrictor "centers" of the spinal cord, medulla oblongata and the brain by afferent fibers, especially the pressoreceptor areas of the arterial tree;
- (2) The cerebral cortex and other cerebral areas acting upon the vasomotor centers;
- (3) The vasomotor centers of the brain, medulla, and cord;
- (4) The peripheral synapses and ganglia, including the adrenal medulla;
- (5) The post-ganglionic neurosecretory sympathetic nerve endings and their respective effector cells.

*Stimuli arising from peripheral tissues*¹⁴⁹³, such as cold temperature, pain, chemical irritations, injury, local infection, distention of the bladder or rectum³⁰⁴³, etc., can provoke reflexory peripheral vasoconstriction (Fig 27, V). Although no conclusive proof is at hand that such stimuli should significantly contribute to major and sustained elevations of the blood pressure, the possibility cannot be flatly denied that self-perpetuating central nervous pressor reactions to the sum of peripheral cellular stimuli of all sorts might gradually build up to a permanent state of central pressor over-irritation⁷¹ in compliance with Speransky's theories²²¹³, which are interesting enough to deserve further study

A disturbance in the function of the pressoreceptor areas of the arterial system has long been suspected as being responsible for some forms of clinical arterial hypertension. A diminution or abolition of the depressor carotid sinus reflex receptivity was theoretically postulated by Hering²¹¹³. The idea of a cessation of function of the sinus nerves in hypertensive individuals could not be substantiated, however, in that manual pressure upon

sinus pressor mechanism. The simultaneous increase of the systolic and diastolic pressure in humans during novocaine blockade of the carotid sinus suggests prevailing nor-epinephrine discharges under these conditions. The accompanying tachycardia is not incompatible with the otherwise bradycardia-producing action of nor-epinephrine, as this latter phenomenon depends on the responsiveness of vagal counter-regulation from the carotid sinus (p. 9) which is completely abolished by the sinus blockade. A certain vagal action must have been maintained in hypertensive individuals, because otherwise no further raise of the blood pressure would occur in such cases during the blockade and tachycardia would be present constantly.

Regardless of the fact that the location of the cerebral, medullary and spinal vasomotor "centers" is only poorly defined, there remains much truth in the statement of E. H. Starling (1925)¹²² regarding the mechanism of neurogenic hypertension: "No pathology will be adequate which does not take into account the sensitiveness of the vasomotor centers to the changes in the circulation."

It has been reported by various investigators that interference with the arterial blood supply to the vasomotor centers leads to a rise in blood pressure.

In addition, experiments carried out by the writer in Dr. Cannon's laboratory in 1930¹²³ showed that the excitability of the vasomotor centers by chemical and reflectory stimuli (inhalation of CO₂ and pain, pressor response, hyperventilation; depressor response) is augmented by hypoxia and by local acidification (Figs. 28, 29, 30, 31). This increase of central vasomotor responsiveness during oxygen deficiency was later confirmed by Heymans^{124, 125, 126} and by Gellhorn and Lambert¹²⁷. It seems that local accumulation of non-oxidized acid metabolites, espe-

FIG. 27. Schematic representation of the vasomotor centers.

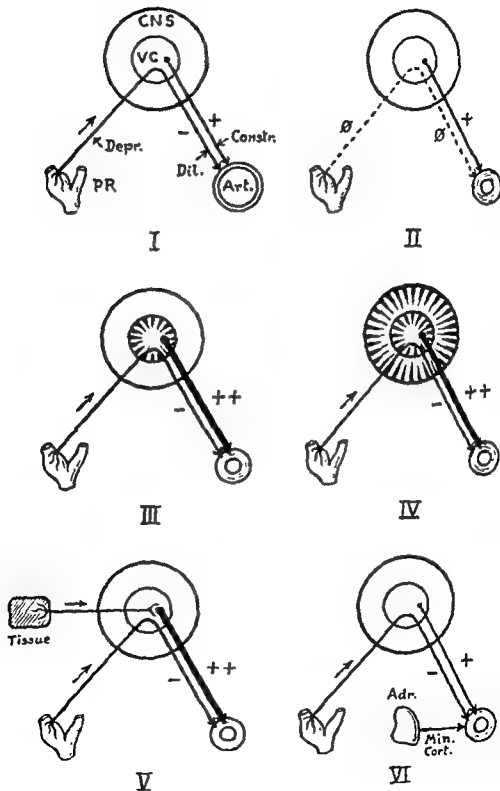


FIG 27

This latter phenomenon which had been described by the writer in 1929²⁵⁰ was confirmed by numerous other workers^{222, 498, 524, 545, 719, 1659, 2740, 3013, 3472, 3475}. It is completely or almost completely absent in normals^{543, 1659, 2648, 2815, 3475} (Fig. 32) and in purely renal hypertension^{739, 2859, 3475} (Table 13). Since the pressor effect of CO₂ is known to occur via the vasomotor cen-

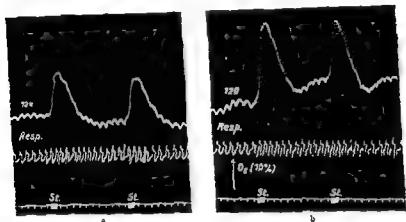


FIG 29 Central pressor responses to peripheral stimuli ("St", crural nerve) increased by hypoxia (a standard conditions, b inhalation of 10 per cent oxygen) in the decerebrate cat

(After W Raab, Arch Int Med 47: 727, 1931)



FIG 30 Central pressor responses to peripheral stimuli ("St", crural nerve) increased by acidification of the brain stem (a standard conditions, b perfusion with lactic acid added to blood) in the decerebrate cat

(After W Raab, Arch Int Med 47: 727, 1931)

ters^{1282, 3418}, it appears probable that the increase in blood pressure to CO₂ inhalation and the increase in blood pressure in hypertensive persons and in hypertension²⁵⁰ are caused by an

The experimental provocation of the cerebral vascular supply^{251, 1372, 2851}, and of accentuated centrogenic vasomotor activity by artificial cerebral arteriosclerosis, and by artificial arteriosclerosis, namely to local vascular

cially lactic acid¹⁸⁵², is responsible for the change in central vasomotor tone and excitability²⁶⁵¹. The systemic pressor effects of central stimulation are mediated by the sympathetic nerves^{1027, 1259} and the adrenal medulla²⁷⁸.

In analogy to the above-mentioned experimental forms of central vasomotor over-responsiveness to certain stimuli, various similar stimuli were

TABLE 12

Response of Blood Pressure and Heart Rate to Bilateral Procaine Blockade of the Carotid Sinus

(After H. Lampen, P. Kezdi, E. Koppermann, and L. Kaufmann, *Ztschr. f. Kreislaufforschg.* 38: 577, 1949)¹⁹⁹¹

CLINICAL CONDITION	BLOOD PRESSURE (AVERAGE)		HEART RATE (AVERAGE)		NUMBER OF CASES
	Before blockade	After blockade	Before blockade	After blockade	
Normal	125/76	207/132	76	132	13
Essential hypertension	192/102	274/147	73	121	9
Malignant hypertension	220/134	321/187	86	136	4

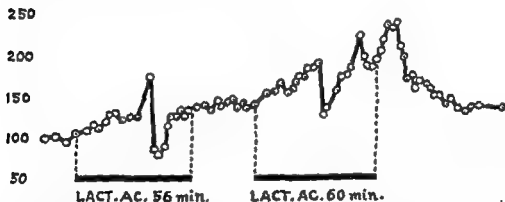


FIG 28 Pressor effect of acidification (perfusion with blood to which lactic acid has been added) of the brain stem of the cat (two perfusion periods of 56 and 60 minutes respectively)

(After W Raab, *Arch Int Med* 47 727, 1931)

found to elicit exaggerated pressor responses also in clinical cases of supposedly neurogenic hypertension, e.g.: (a) inhalation of CO_2 ^{1271 2656 2945} and breath-holding^{105 1314}, (b) pain, such as that produced by cooling of one hand in ice water^{104 1271 1512 2177} and other measures⁹¹⁵, (c) inhalation of ammonia²⁰. Intensified depressor reactions, on the other hand, were observed (a) after administration of barbiturates^{21 1254 1357}, (b) following spinal puncture¹⁶⁹⁰ and anesthesia^{1781 1619a} and (c) during hyperventilatory loss^c of CO_2 (Fig 33).

This latter phenomenon which had been described by the writer in 1929²⁶⁵⁰ was confirmed by numerous other workers^{323, 406, 423, 435, 735, 1434, 2740, 3113, 3472, 3476}. It is completely or almost completely absent in normals^{323, 1455, 2646, 3018, 3475} (Fig 32) and in purely renal hypertension^{735, 2655, 3475} (Table 13). Since the pressor effect of CO_2 is known to occur via the vasomotor cen-

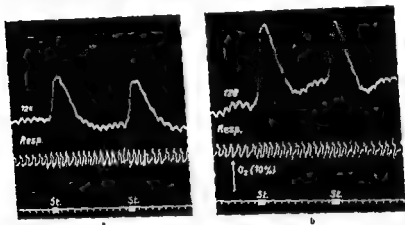


FIG 29 Central pressor responses to peripheral stimuli ("St."; crural nerve) increased by hypoxia (a standard conditions, b inhalation of 10 per cent oxygen) in the decerebrate cat
(After W Raab, Arch Int Med 47 727, 1931)



FIG 30 Central pressor responses to peripheral stimuli ("St."; crural nerve) increased by acidification of the brain stem (a standard conditions, b perfusion with lactic acid added to blood) in the decerebrate cat
(After W Raab, Arch Int Med 47 727, 1931)

ters^{205, 3445}, it appears probable that both the intensified pressor response to CO_2 inhalation and the intensified depressor effectiveness of CO_2 loss in hypertensive persons and in animals with artificial centrogenic hypertension²⁶¹ are caused by an abnormal sensitivity of the vasomotor centers

The experimental provocation of hypertension by ligating the cerebral vascular supply^{407, 1422, 2651}, and of accentuated centrogenic pressor responses by artificial cerebral hypoxia and acidification^{1122, 1434, 2651} suggest that certain forms of hypertension, e.g. those with demonstrable cerebral arteriosclerosis, owe their existence to a similar condition, namely to local vascular

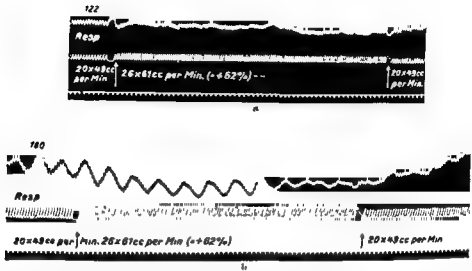


FIG. 31. Central depressor effect of (artificial) hyperventilation (from \uparrow to \downarrow) increased in the decerebrate cat, made hypertensive by acidification of the brain stem *a* Standard conditions; *b* Perfusion with lactic acid added to blood. The respiratory movements appear larger in the second graph due to a change in position of the lever, but they were actually analogous in both experimental periods *a* and *b* (After W. Raab, Arch Int Med 47:727, 1931)

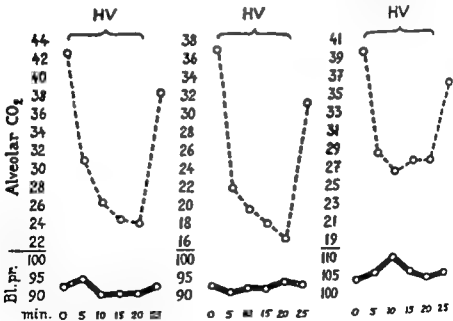


FIG. 32. Response of alveolar CO₂ and systolic blood pressure to hyperventilation (HV) in three normotensive individuals. Compare with Fig. 31 *a*. (After W. Raab, Ann Int Med 14:1981, 1911)

ischemia and hypoxia of those cerebral and medullary areas which are responsible for peripheral vasoconstriction by means of sympathetic neuro-

hormonal discharges. Ischemia-producing arteriolar sclerotic lesions have been observed frequently, though not without exception, in the cerebral stem ganglia⁴³, medulla oblongata and other cerebral and medullary areas of hypertensive individuals (lit., see⁴⁴, also ^{412, 441, 494, 1224, 2273, 2292, 2174, 2497}).

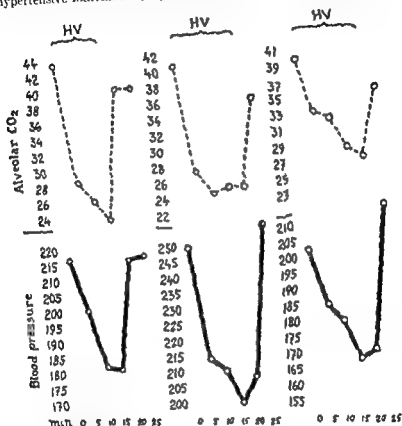


FIG. 33. Response of alveolar CO₂ and systolic blood pressure to hyperventilation (HV) in three patients with "essential" hypertension. Compare with Figs. 31 a, b and 42.

(After W. Raab, *Ann Int Med* 14 1981, 1911)

^{258, 2425} Even in early hypertension, characteristic proliferation and degenerative changes of the brain capillaries were described²⁵⁸. They were not paralleled by analogous lesions in the kidneys.

Findings obtained by the writer in 1930 and indicating an increased arterio-venous oxygen difference in the brain blood of hypertensive subjects²⁶², are of only limited conclusiveness regarding an assumed decrease of cerebral blood flow. Kety and Schmidt, who used the more informative nitrous oxide method, recorded a diminished blood flow and oxygen con-

sumption in the brains of one group of hypertensive patients¹⁷⁸³ in agreement with similar findings of Scheinberg²⁹⁶⁷; but in another series no significant abnormalities were found¹⁷⁶². A decreased blood flow through the brain was observed in uremic patients with severe hypertension¹¹⁹².

Results of the optical "flicker fusion test" were interpreted as indicating cerebral hypoxia in hypertensive subjects⁵⁷⁸ and diminutions of the blood pressure level during diathermy of the skull^{1927, 2653} suggested a temporary improvement of cerebro-medullary circulation.

In general, a reduction of the caliber of the total cerebral vascular bed takes place with advancing age^{612, 1324, 1761, 2592, 2664}. It is paralleled by a gradual increase of the average pressor response to CO₂ inhalation^{2634, 2668} (Fig. 34) and to cold stimuli^{95, 2902}, especially in the presence of marked

TABLE 13

Response of Systolic Blood Pressure to Hyperventilation in Normotensive and Hypertensive Patients
(After W. Raab²⁴⁴⁴)

TYPE OF CASES	NUMBER OF TESTS	AVERAGE SYSTOLIC BLOOD PRESSURE LEVEL	AVERAGE DEVIATION OF SYSTOLIC BLOOD PRESSURE DURING HYPERVENTILATION
		mm Hg	mm Hg
Normal	15	100	± 0
Acute glomerulonephritis	6	163	± 0
"Essential" and nephrosclerotic hypertension.	40	198	-30

cerebral arteriosclerosis⁹⁵, and by a decrease of the critical flicker frequency²³⁴⁴

Hypoxia-sensitivity of the cerebro-medullary vasoconstrictor centers is a well established fact. So is the frequent co-existence of cerebral arteriolar sclerosis with hypertension. What we do not know is the exact location and distribution of the central areas which are responsible for peripheral vasoconstriction. The fact that not all individuals with post-mortem demonstrable cerebral arteriosclerosis had also hypertension²³⁷⁸ may be due to the irregularity in the distribution of the arteriolar lesions which may or may not affect the specific vasomotor areas (Fig. 27, III). It is virtually unthinkable, however, that diffuse cerebral arteriolar sclerosis should spare the vasomotor center areas in all cases. If and when it does involve these areas, it would seem equally improbable that the hypoxia-sensitive centers should not respond with an elevation of the systemic blood pressure, unless other counterregulatory factors interfere. In one case of extreme hyperten-

sion (320/160), autopsy revealed a complete obliteration of the basilar artery^{902a}

Acute emotional excitement is accompanied by pressor reactions of the epinephrine type^{182, 812, 1581, 1602, 2254}. This seems to be true in particular in individuals who give vent to their feelings during mental stress. Their cardiac output was found increased and the peripheral resistance lowered, while the blood pressure rose^{1661a}. On the other hand, mental stress, induced in persons who tried to suppress their emotional reactions, was accompanied by elevations of the blood pressure, caused by an augmentation of

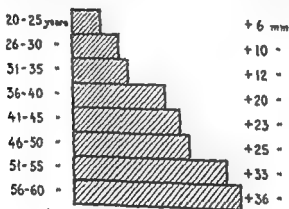


Fig. 21. Increase in blood pressure with age.

(after W. Raab, Ann Int Med 14, 1991, 1941)

the peripheral resistance^{1661a}, which suggests a preponderance of nor-epinephrine action. Renal vascular resistance was likewise increased^{1661a}. Indications for a prevailing epinephrine activity were observed in manic-depressive cases while a prevalence of nor-epinephrine effects was concluded from the reactions of schizophrenic patients^{1099a}. Certain personality patterns with "obsessive-compulsive" tendencies, "sub-normal assertiveness", anxiety states, frustrations and suppressed hostilities are said to form the central nervous background for the development of neurogenic hypertension^{17, 101, 244, 810, 1061, 1270, 1321, 2210, 2779, 2947, 3010, 3270}. Prolonged sensory impulses may produce hypertension in animals^{341, 2258}. "blast hypertension" was described as an aftermath of the Texas City disaster among the survivors²⁹⁹⁷, and elevations of the blood pressure could be induced in hypnosis²⁷⁵⁹. On the other hand, the blood pressure of schizophrenic individuals is usually

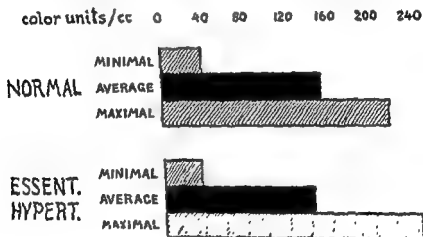
rather low and hypertension is only rarely encountered in them^{1015, 1321}. It is generally assumed that the pressor effects of cortical and subcortical stimuli are conveyed by the cerebromedullary vasoconstrictor centers (Fig. 27, IV).

The presence in all parts of the brain and in the spinal fluid of an epinephrine-like pressor amine, designated by the writer as "*encephalin*"²⁸³, ²⁸⁴ (p. 351, 352), raises the question as to whether neurosecretory discharges from the brain into the circulation might not participate in the mechanism of emotional hypertension²⁸¹. A similar concept was more recently adopted also by Talor and co-workers³³⁴ who confirmed the observation of Spanish investigators^{708, 1060} that stimulation of the central stump of the vagus nerve is followed by the appearance of a pressor substance in the circulation. The so-called "*hypertensive diencephalic syndrome*", described by Page²¹⁹, consists of neurovegetative and emotional outbursts and occurs mostly in young or middle-aged women. It is accompanied by a high basal metabolic rate³⁴⁴, can be provoked by intradermal injections of histamine³⁰⁴⁰, and is amenable to treatment with barbiturates³⁴⁴. It resembles the attacks of "*diencephalic epilepsy*"⁷²⁵⁰ and of pheochromocytomatous crises, thus clearly pointing toward a cerebral origin with neurohormonal discharges. The underlying diencephalic condition has been ascribed to local arteriosclerotic changes and edema³⁹⁰³ which can appear acutely³⁷⁰.

The lability of blood pressure in the early stages of essential hypertension and its wide range of variations^{100, 101, 111, 1314, 1331, 2749, 3038, 3177} were taken by some workers as indications of its central nervous origin. A pathogenic role of nervous mechanisms was also concluded from the estimated regional distribution of vasoconstriction in hypertensive individuals^{7, 1194, 3254}. Whether some peculiar proliferative vascular changes, which were found within the sympathetic ganglia of patients with severe hypertension¹⁹²⁹, are of any functional significance regarding peripheral sympathetic neurosecretion into the vascular walls cannot be decided at the present time. No characteristic alterations could be detected in the ganglionic cells themselves^{233, 2221}.

Since the role of the sympathetic nervous system in the origin of a large percentage of cases of "*essential*" hypertension seems reasonably well established, it can almost be taken for granted that *nor-epinephrine and/or epinephrine as the sympathetic neurohormonal transmitters*^{905, 1554} are fundamentally involved in the process of abnormal blood pressure elevation. The results of the age-long search for increased epinephrine levels in the blood of patients with essential hypertension were disappointing in that they brought to light a variety of pressor substances of doubtful pathogenic significance (lit., see^{1263, 3040}), but no proof of an increased amount of circu-

lating epinephrine^{1965, 1591, 1691, 2162, 2570, 2477, 2575} with the exception of a few technically questionable positive findings^{1120, 1968}. Observations of Kunschegg^{1813, 1816, 1818} indicated that the blood of essential and renal hypertensive patients contains amounts of epinephrine which, although quantitatively within normal range, are abnormally stable and active, due to compound formation with certain blood lipids. Unfortunately these interesting findings have not yet been taken up by other workers. Colorimetric determinations by the writer²⁶⁴² yielded consistently normal resting values in 25 patients with essential hypertension (Fig. 35) while physical exercise was followed by a moderately increased average rise of these substances



... .., *Arch. Int. Med.* 65: 713, 1941)

within two minutes (Fig. 36), suggesting an exaggerated neurosecretory excitability. In the case of a two-year-old infant with biologically normal adrenal glands and high unstable blood pressure levels, the fluctuations of the catechol concentrations in the blood paralleled roughly the systolic blood pressure changes (Fig. 37).

A reported increase of "urosympathin" (mixture of nor-epinephrine

epi-
hols
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... .. assay of epinephrine and nor-epinephrine in blood and urine will ever prove a completely satisfactory approach to the problem of neurogenic essential hypertension, since the decisive neurosecretory process takes place inside the contractile cardiovascular tissue. The bulk of the responsible neurotransmitters can be expected to enter the

blood circulation, if at all, only in a partially degraded form, as far as they have not entirely lost their catechol character by being oxidized to adrenochrome and other quinones¹⁷⁶ within the effector cells. The findings of an increase of the catecholamine concentration in human arterial walls of aged

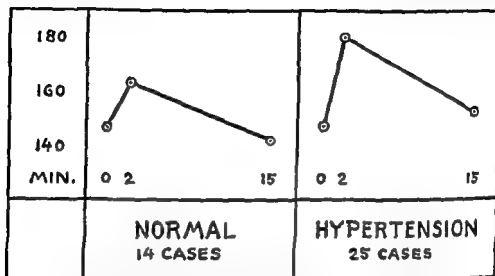


FIG 36 Average catecholamine concentrations in the blood of 14 normal and 25 hypertensive individuals before, two, and 15 minutes after a standard exercise test (After W Raab, *Ann Int Med* 28 1010, 1948)

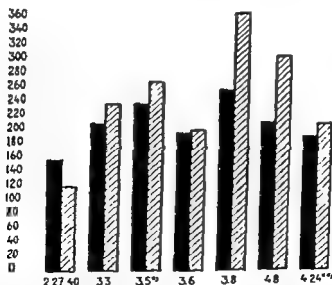


FIG 37 Fluctuations of systolic blood pressure (black bars) and catecholamine concentration of the blood (shaded bars) in a two-year-old infant (suspected but not verified pheochromocytoma) *After massage of right suprarenal region, **during general anesthesia (Method, see p 4, 5) (After W Raab, *Ann Int Med* 14 1981, 1941)

individuals²⁶⁷⁴ and in the majority of the hearts of hypertension victims²⁶⁷⁰ may serve as indirect indications of augmented sympathogenic neurosecretory discharges into the cardiovascular tissue.

The neurosecretory products of sympathetic post-ganglionic fibers consist preponderantly of nor-epinephrine rather than of epinephrine^{265 2334}. This fact which was established specifically for the arterial walls²⁶¹⁷, makes nor-epinephrine appear the predestined agent to maintain the high blood pressure level of neurogenic hypertension. The striking clinical similarities between the entire cardiovascular and renal syndrome of nor-epinephrine-secreting pheochromocytoma with sustained hypertension on one hand (p 78, 83) and that of essential hypertension on the other have been pointed out by several authors^{1177 1194 1214 2718 3030}. Perhaps the most important argument in favor of a dominant role of nor-epinephrine in neurogenic hypertension is the virtual identity of the hemodynamic effects, produced by infusion of nor-epinephrine, and the hemodynamic situation prevailing in essential hypertension. The effects of sympatholytic drugs and of sympathectomy in essential hypertension will be discussed on pp 293 ff., 299 ff. and 303.

Jiménez Díaz and his associates^{793 1440} have demonstrated the "internal secretory" discharge of precursor material from the arterial walls into the circulation under the influence of central nervous stimuli. In contrast to their earlier views, the Spanish investigators are now inclined to identify this material, at least in part, with nor-epinephrine¹⁴³³.

According to findings obtained with modern techniques^{340 4131}, the increase in total peripheral resistance, which had long been known to exist in essential hypertension^{447 1383 2769 2813 3012}, is in general associated with a normal cardiac output. These hemodynamic conditions, as well as an elevated diastolic pressure, represent the exact analogy to the hemodynamic effect of infused nor-epinephrine which acts as an over-all vasoconstrictor, raises both the systolic and the diastolic pressure, does not produce any significant increase of the cardiac output and retards rather than accelerates the heart beat^{139 171 1140 1334 2704 2727} in contrast to epinephrine. One objection, which has been raised against a full identity of nor-epinephrine action and the mechanism of neurogenic essential hypertension, is the augmentation of the mean pressure in the pulmonary artery^{1 2}.

the va-

... the blood stream, while spontaneously acting neurogenic nor-epinephrine stimulates only those vascular areas into whose arterial walls it is directly discharged by their respective supplying sympathetic fibers

blood circulation, if at all, only in a partially degraded form, as far as they have not entirely lost their catechol character by being oxidized to adrenochrome and other quinones¹⁷⁷⁶ within the effector cells. The findings of an increase of the catecholamine concentration in human arterial walls of aged

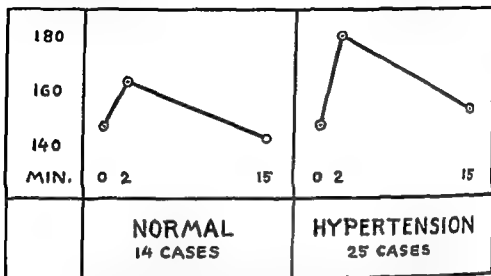


FIG 36 Average catecholamine concentrations in the blood of 14 normal and 25 hypertensive individuals before, two, and 15 minutes after a standard exercise test (After W. Raab, *Ann. Int. Med.* 28: 1010, 1948)

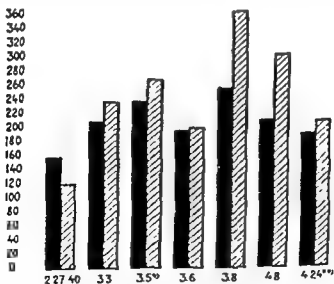


FIG 37 Fluctuations of systolic blood pressure (black bars) and catecholamine (hatched bars) across various time points

effectiveness (e.g., epinephrine-lectin complexes^{2157, 2445}) or both, appears a possibility, in view of the experimentally proven renal blood flow-diminishing effect of epinephrine^{134, 1929, 2181} and nor-epinephrine^{2281a}. Besides, the ischemic kidney tissue has been found to permit the formation of excess amounts of vasoactive hydroxytyramine from dihydroxyphenylalanine^{267, 1359}, thus possibly participating itself in the establishment of a vicious circle to the detriment of its vascular status. None of these speculative assumptions of a possible locally nephrotoxic activity of the adrenosympathogenic neurohormones, their precursors (hydroxytyramine, adrenalinogen), lipid compounds and catechol derivatives, has yet been clearly proven. However, there exists so much factual evidence for a deleterious chemical influence of catecholamines upon cardiovascular tissue (p. 11, 15) that the possibility of harmful effects also upon the renal vessels seems to deserve serious consideration. The fact alone that severe functional (though reversible) and later arteriolar sclerotic lesions of the kidneys in cases of pheochromocytoma are common events (p. 83, 86) points emphatically in this direction.

In the average case of essential hypertension, it takes usually years of the hypertensive state before clinically demonstrable functional renal excretory derangements^{647, 853, 992, 1189} become apparent as a secondary development or before morphological vascular lesions can be detected at biopsy⁴⁹⁰. In a sizable percentage of cases of essential hypertension, the kidneys were found free of sclerotic changes, even at necropsy^{490, 691, 979, 982, 1184, 1296, 1690, 2104}. There is reason to agree with the opinion of those who consider renal arteriolar sclerosis neither as the dominating cause nor as a direct sequel of high blood pressure^{929, 942, 2224a}, but rather as a partially independent accompanying condition which seems to share with the hypertension its pathogenic background, namely an adrenosympathetic neurosecretory over-activity with its pressor and hypoxiating destructive effects.

Once a major degree of vascular renal ischemia sets in, the Goldblatt type of nephrogenic hypertension, whatever its humoral nature may be, will complicate the situation and may ultimately entirely overshadow or replace the original neurohormonal pressor mechanism. The malignant phase of renal hypertension will be discussed separately (p. 310 ff.).

It has been shown that ————
regardless of severe

hypertension is likewise

(lit., see 1172). On the other hand, renal ischemia, either of nervous vasoconstrictory¹⁹¹⁸ or mechanical⁹⁶⁸ origin, seems to initiate the secretion of renin in increased quantities⁹⁴⁸. The juxtaglomerular apparatus is suspected to be ————

Thus, a reflectory or centrogenic neurosecretory nor-epinephrine interference in arterial wall tonicity can be accepted as a well founded probability for the ordinary forms of neurogenic essential hypertension. Nevertheless, there seems to exist one group of cases in which certain features point toward a preponderance of epinephrine action. These systolic hypertensive patients display an increased stroke volume, accelerated heart action, small arterio-venous oxygen difference and a relatively low diastolic pressure^{712, 859, 1417, 1842}. They have been designated as cases of "minute-volume hypertension" (lit., see²⁷⁶⁹) and display all the earmarks of epinephrine activity with its general vasodilating effect^{1130, 2767}, increased cardiac output^{110, 1211} and lowered diastolic pressure^{856, 1648, 2704}. These individuals are also likely to have an elevated basal metabolic rate without demonstrable thyroid involvement (lit. see²⁷¹⁹). This is probably to be interpreted as an expression of the calorogenic activity of the sympathomimetic catecholamines, especially of epinephrine^{733, 1274}, which is said to be much more effective in this respect¹⁵⁸⁵ than nor-epinephrine. Whether the presumably exaggerated amounts of epinephrine, acting in this category of hypertension, derive from the adrenal medulla or also from sympathetic fibers is not known.

The arterioles of the kidneys constitute a section of the arterial system in which adrenosympathogenic catecholamine action is probably of particularly fateful importance because it may contribute to a further aggravation and ultimate stabilization of the hypertensive state.

It would be beyond the scope of this treatise to enter into a detailed discussion of the problem of renal hypertension, but certain points concerning correlations between neurohormonal and renal pressor mechanisms should be briefly mentioned.

For evaluation of the part played by a diminution of renal blood flow in the development of renal hypertension, it is of significance that electrical^{1263, 1268, 1692, 1827, 2790} and chemical^{2947, 3168} stimulations of the nerves of the kidneys cause constriction, especially of the efferent glomerular arterioles and that this constriction may persist for an hour or longer after termination of the respective stimulus³¹⁶⁶. Emotional excitement is likewise accompanied by a diminution of renal blood flow^{3166, 3661, 3662a} which can be abolished by sympathectomy²⁹¹⁰. In chronic clinical essential hypertension, a functional reduction of effective renal blood flow occurs with great regularity¹¹⁴⁴, except in the earliest stage⁵³⁹. This increased tonicity of the efferent arterioles is reversible, e.g., by the administration of pyrogens¹¹³⁵, but does not necessarily disappear after renal denervation²⁵⁰⁷ or sympathectomy⁵⁵⁷ so that a humoral mechanism was held responsible for it⁵⁴⁷. An injurious effect of the contact of the renal arterioles with circulating sympathogenic catecholamines, either in increased amounts or in a state of increased vasoconstrictor

in part dependent on the dosage. The systolic pressure may rise^{1251, 1491} or fall^{130, 707, 906, 1180, 1251, 1303, 1391, 2191}, according to the balance between the cardiac stimulating, vasodilating and vasoconstricting actions of epinephrine. The diastolic pressure is usually depressed by small doses, while larger doses tend to elevate also the diastolic level. *Nor-epinephrine* was described as producing a distinctly greater systolic and mean pressure elevation in hypertensive subjects, as compared with normotensives¹¹⁹⁰. Other workers²⁵⁰⁵ found its effect about normal.

A brief review of the different types of stimuli which can be assumed to produce *neurogenic hypertension* indicates the three following as those most likely to be involved in the pathogenesis of clinical essential hypertension: (1) emotional stimuli (via sympathetic pathways, encephalin²); (2) increased excitation and excitability of cerebral and medullary vasoconstrictor centers, due to local arteriolar sclerotic ischemia and acidification, (3) preponderance of sympathetic cardiovascular tonus because of diminished vagal counter-regulatory reflexes from the insufficiently distensible carotid sinus. In the two first instances, an absolutely increased neurosecretion of prevalingly *nor-epinephrine* into the muscular cardiovascular cells can be considered as probable, in the third the neurosecretory activity of the sympathetic postganglionic fibers may be quantitatively normal, but disproportionately effective in the absence of adequate cholinergic counteraction. Another important possibility of exaggerated adrenergic cardiovascular dynamic effectiveness is suggested by the phenomenon of an abnormally potentiated pressor action of epinephrine and *nor-epinephrine*, due to interference of the adrenal mineralocorticoids (DCA). This question will be discussed in the following section.

Role of the Pituitary-Adrenocortical Axis ("*Hormonal Hypertension*")

Experimental evidence (p. 15) and clinical pathological observations in pituitary overfunction (p. 164) make it appear unlikely that anterior pituitary hormones exert any significant direct pressor effects upon the cardiovascular system. Marked deviations of the blood pressure from normal, such as the hypertension in Cushing's disease and the hypotension in hypopituitarism, are probably attributable to these and ...

... description of the syndrome which combined so impressively a demonstrable anomaly of the pituitary with arterial hypertension. Cushing's suggestion that an invasion of the posterior lobe by basophil cells from the adenohypophysis might somehow activate the secretion of vasopressor posterior lobe hormone²²⁵, was accepted by some and

mechanism of the vast majority of cases of essential hypertension^{19, 736, 767, 1253, 1422, 2412, 2501}. The functional implications of the enlargement of the adrenal medulla in experimental renal hypertension²⁷⁴⁶ have not yet been investigated.

Despite the deflation of the renin theory, there is no dearth of *vasopressor substances*, which have been claimed with more or less justification to occur in abnormally large quantities in the blood, urine or tissues of hypertensive individuals and to play a part in the pathogenesis of essential hypertension. Schroeder³⁰¹⁰ lists 16 such substances, including nor-epinephrine and uro-sympathin. The series might be enlarged by Westphal's "hypertonin"¹⁷⁶⁷³, a pressor substance, obtained from the blood of hypertensive patients and of rabbits with neurogenic (intracisternal kaolin) hypertension³⁷⁷⁶, supposedly of adrenal origin; a posterior pituitary hormone-like substance³²² and others, described in the older literature¹³⁶⁹; also more recently, Enger's "nephrin" which was extracted from kidney tissue and from the blood of hypertensive dogs and humans but not from that of normotensive individuals^{573, 673}. In the present discussion, we are interested only in those pressor substances which can be considered as being possibly related in one way or another to the adrenosympathetic pressor neurohormones. Schroeder's "pherentasin"³²⁴⁹ is a chemically unidentified substance, supposedly a primary amine, which was found only in the blood of hypertensive persons, although prevailing in those with renal damage⁷⁰⁴⁰. Its pressor effect is prolonged and not inhibited by dibenamine⁶⁷⁷, thus different from that of nor-epinephrine. It displays certain similarities of action with Shorr's VEM ("vaso-excitator material")^{3125, 3723}. The latter, whose chemical nature is also unknown, sensitizes the terminal vascular bed of the rat mesoappendix to the constricting effect of topically applied epinephrine. It originates in the ischemic kidney and is found in the blood of animals with experimental renal hypertension, as well as in that of humans with chronic essential hypertension. In the latter it is counteracted by increased amounts of VDM ("vaso-depressor material", ferritin)²²⁶⁹. It acts in a similar fashion regarding nor-epinephrine³¹²⁶. Whether it contributes to the elevation of blood pressure in essential hypertension, is not known.

Page and co-workers²⁵⁰⁶ and Harrison, Grollman and Williams¹²⁹⁵ isolated antipressor substances from the kidney and Wollheim³⁶⁷⁸ from the urine. This latter urinary substance ("depressan"), was found to be diminished in patients with essential hypertension^{2356, 3671}. There are no indications, however, that "depressan" interferes specifically with neurohormonal pressor mechanisms³⁶⁷⁴.

The *blood pressure response* of patients with essential hypertension to subcutaneously injected or intravenously infused epinephrine is irregular and

adrenocortical axis. No clear-cut borderlines can be drawn through this intricate maze of mutual interactions. Attempts to regard the problem of essential hypertension in terms of a postulated degenerative under-function of the hypothalamus and an equally unproven under-function of the posterior pituitary, supposedly causing over-function of the anterior lobe eosinophil cells^{141, 142}, are at variance with most accepted views and cannot be incorporated in our further reasoning until strengthened by supportive evidence.

Proof for an exaggerated adrenal cortical function in essential hypertension was long sought on the grounds of morphological criteria. It appeared to be suggested by a relatively frequent occurrence of hyperplasia or adenomas of the adrenal cortex in individuals with essential hypertension, as recorded by many observers^{30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140}. These findings seemed to point toward possible analogies with the hypertension existing in Cushing's syndrome. However, the specificity of such changes for essential hypertension was emphatically denied by other workers^{147, 148}, and there seems to be little hope to arrive at definite conclusions on the basis of purely morphological criteria.

Greater importance can perhaps be attached to the presence of increased amounts of lipids in the adrenal cortex of individuals with essential and renal hypertension⁹⁹. This increase was found by Kutscher-Aichberger

the dir... contrast to opposite conditions seen during states of adrenal cortical exhaustion¹⁴². No direct conclusions regarding the intensity of hormone production can be drawn from these findings, but they throw an interesting light on cortico-medullary relations in view of the presumable formation of stable and potent epinephrine-phospholipid compounds¹⁴⁴, which were found to circulate in the blood of hypertensive individuals^{145, 146}.

Direct hormone assays and functional tests concerning cortical activity in essential hypertension have been carried out only on a limited basis.

instances¹⁴⁹. Phosphomolybdate-reducing steroidal compounds were likewise increased in the urine¹⁴⁹. A somewhat intensified excretion of

rejected by others (lit., see ¹⁵⁹⁶), but this primarily morphological problem lost a great deal of its interest when methods for hormone assay came into being. The accuracy of these older techniques is questionable, however, and claims regarding the presence of an increased amount of posterior lobe hormone^{154, 112, 2557}, of excess corticotrophic hormone^{741, 1678} and of gonadotrophic hormone in the blood and urine¹⁸³¹ of hypertensive patients can hardly be accepted at face value. Not even today are satisfactory methods for the quantitative clinical estimation of the adrenocorticotrophic hormone (ACTH) and the somatotrophic hormone (STH) available. Thus, while a prominent role of the pituitary in the pathogenesis of essential hypertension appears as a definite possibility, there is little positive evidence to be referred to in its favor.

Much that was said about the part played by the pituitary in the origin of arteriosclerosis (p. 256) applies likewise to the problem of essential hypertension, largely because of the habit of earlier workers to identify hypertension with arteriosclerosis. It should be understood, however, that arteriosclerosis and hypertension, although apparently developing on a common hormonal pathogenic basis, and although eventually merging into a mutually aggravating partnership, are essentially independent morbid entities.

Despite the existing uncertainties concerning details of *pituitary function in connection with essential hypertension*, it seems justified in the light of ample experimental evidence to assume that over-activity of the anterior lobe as pertaining to the endocrine pattern of the "alarm reactions" of daily life, may well give rise to exaggerations of adrenocortical function. These, in turn, would initiate hypertension at least in the one sub-group of essential hypertension which is termed as "endocrine", as distinguished from the neurogenic types. It must be kept in mind, however, that in view of the various interrelations of pituitary-cortical function on the one hand with the adrenosympathetic system and the hypothalamus on the other, any such verbal distinction is to be regarded as somewhat artificial and merely intended to indicate the more or less conspicuous prevalence of either hormonal or neurohormonal factors over their respective counterpart in the individual case.

Hypothalamic involvement of one kind or another can be assumed for both the neurogenic and hormonal types of essential hypertension. In the former, the hypothalamus serves as the seat or relay area of central vasoconstrictor mechanisms under extra- and intracerebral reflectory and cerebral cortical control, in the latter as a receptor of neurohormonal (epinephrine) stimuli from the periphery and of emotional intracerebral stimuli (encephalin?), which are translated into cerebral stimulation of the pituito-

tory volume cannot be made responsible as it was found to be only of a minor degree²⁹⁴ or entirely lacking²⁹⁵. Water retention under DCA influence is usually a transient effect, limited to the first 7-10 days of DCA administration^{1243, 2461, 2905}, whereas the hypertensive state continues.

Even during the phase of sodium retention, the blood sodium levels are^{1243, 2461, 2905} as they are in this fact was believed to be the mechanism of DCA hypertension²³⁷¹ and by the same token also of essential hypertension²⁵⁶⁷, it must be re-emphasized that blood sodium levels per se are an inadequate criterion for evaluation of the more important conditions in the tissues. The one specific effect of DCA (and probably other mineralocorticoids) which seems to be of primary significance for its influence upon cardiovascular dynamics, is the alteration of intra- extracellular electrolyte balance, especially the DCA-induced intracellular accumulation of sodium^{144, 145, 147, 148, 2430, 2691} which can be assumed to result in changes of the electrical membrane potentials in the vascular musculature^{1600, 1692}. The intensification of pressor action of DCA by a simultaneous intake of sodium chloride^{1074, 1217, 1320, 1792, 2244, 2799} and its weakening or abolition by salt withdrawal^{1463, 2020, 2913, 2993} are well established facts. The striking reduction of the blood pressure level in some cases of essential hypertension under a sodium-poor regime (p. 304 ff), makes it probable that the sodium ion is involved in the mechanism of hypertension in a similar fashion. Further support for this concept seems to be furnished by the recent finding¹⁴¹³ of a significantly increased sodium content of the arterial walls of hypertensive patients. The total body sodium in hypertensive individuals was also found slightly augmented^{1572a}, in apparent agreement with experimental observations^{2324a}.

Earlier observations of the writer and his co-workers^{2461, 2766, 2714} and of others^{2094, 2942} have shown that in normotensive subjects the pressor effects of injected or infused epinephrine and nor-epinephrine are regularly increased after pre-treatment with DCA before the resting level has even begun to rise (p. 23 ff). On the other hand, it was noticed²⁷⁰⁵ that the pressure ceilings, produced by infused epinephrine and nor-epinephrine, were markedly lowered during periods of sodium withdrawal, that the pressor effect of the catecholamines was somewhat

the pressor action by potentiating the pressor effectiveness of the intrinsic catecholamines (notably nor-epinephrine) which are con-

nificance for the pathogenesis of hypertension than the mineralocorticoids, except for their supposed antagonistic action against the latter, the aforementioned results do not contribute any essential information.

Fractionated determination of 11-oxy- and 11-desoxycorticoids^{256a} revealed a proportionate absolute augmentation of both constituents in the urines of one series of patients with essential hypertension.

An important clue is furnished by findings obtained with the method of sodium determination in thermal sweat, since the sodium concentration is directly influenced by mineralocorticoid action⁵⁷³. A low sodium concentration in the sweat of hypertensive patients has been described^{574, 2567}. In one series, published by Davies and Clark⁵⁷⁴, approximately 20% of the hypertensive cases displayed this peculiarity, while the values for the rest were within normal range. The hypertensives who presented a low sweat sodium, suggestive of increased mineralocorticoid activity, were usually also distinguished by certain clinical characteristics, reminiscent of Cushing's syndrome, such as a more or less rapidly developing central obesity and menstrual abnormalities. They are considered by Schroeder²⁵⁶⁸ as a special subgroup of essential hypertension and designated as "pseudo-Cushing's syndrome"¹⁹³⁰³¹. Up to the present, this is the only type of hypertension other than that occurring in true Cushing's syndrome for which an absolute over-activity of the adrenal mineralocorticoids could be made probable by direct functional evidence.

Whether a *relative preponderance of mineralocorticoid activity* over a relatively deficient function of supposedly antagonistic glucocorticoids, contributes to the pressure elevations of essential hypertension cannot be decided on the basis of available information. Some observations concerning a depression of hypertensive pressure levels by cortisone^{2572, 2573} or by glucocorticoid-containing adrenal cortical extracts²⁵⁶⁶, seem to parallel an apparently antagonistic action of adrenal cortical extracts against the pressor effect of injected DCA in hypertensive individuals²⁵⁷⁴. However, other workers^{510, 2721a} were unable to duplicate such effects either with Cortisone or ACTH. Hypertensive persons develop blood pressure rises more readily than normals under the influence of DCA injections, administered during several days²⁵⁷¹ or weeks²⁵⁶⁴. In cases of hypertension, both acute and prolonged slight to moderate elevations of the blood pressure were observed after intravenous injection of a single dose of DCA, in contrast to the non-responsiveness of normotensive subjects¹¹⁸⁶ to such dosage.

The hemodynamic behavior of DCA-induced hypertension resembles that of both nor-epinephrine action and of the common type of essential hypertension in that the peripheral resistance is increased²⁹⁴³ without a simultaneous increase of cardiac output^{1196, 2943}. An augmentation of the circula-

pressor agent in conjunction with DCA^{1056, 1247, 1306, 1792, 2244, 2301}, seems to rest in the fact that only a simultaneously intensified action of mineralo-

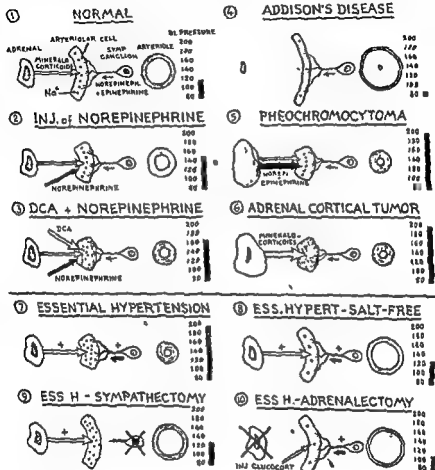


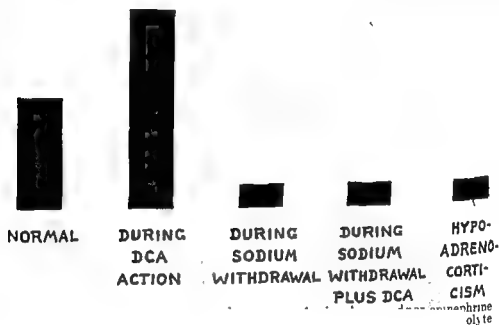
FIG 39

W. D. HALL, 1952

corticoids²⁵⁷⁶ will permit the entry of sodium into the vascular cells in sufficient amounts to augment their contractile responsiveness to their own intrinsic catecholamine supply (Fig 27, VI) This principle is illus-

stantly present within the contractile elements of the cardiovascular musculature, (b) that this potentiation is mediated by the intracellular deposition of sodium under the direct influence of DCA. The resulting alteration of the intra-extra-cellular electrolyte concentration gradient which is believed to affect the electric membrane potential of the contractile cells, determines the magnitude of the contractile effect of depolarizing pressor agents, such as nor-epinephrine and epinephrine.

PRESSOR EFFECTIVENESS OF CATECHOLAMINES



This concept, although in need of further confirmation of some of its basic assumptions, has been applied to the explanation of the blood pressure changes in hyperadrenocorticism, pheochromocytoma and Addison's disease (Fig. 39). It appears suitable also for the understanding of various mechanisms, operating in different types of essential hypertension. Since it integrates the combined physiological effects of sympathetic neurosecretion and mineralocorticoid activity with sodium as the obligatory mediator²⁶⁰, it would fit a variety of situations, all of which result in analogous pressor effects (Table 14).

The reason why excessive sodium intake alone exerts little or no influence on the blood pressure level^{1293, 1300, 2563, 2925, 2943} while it acts as a strong

the pressor responses to sympathomimetic catecholamines: augmentation by DCA, weakening by salt withdrawal.

It can be concluded from observations on adrenalectomized animals that changes in the electrolyte balance affect not only the pressor responsiveness to the catecholamines, but also to other pressor agents, such as pitressin¹⁵⁵ and injected renin^{156, 196, 277}, and to the humoral pressor stimuli of experimental renal ischemia²⁷⁸. This latter point is of interest in that it would explain the therapeutic results, even though limited, of a salt-free diet (p. 317) and of bilateral adrenalectomy (p. 318) in some patients with prevalently or partially renal hypertension. The vasoconstrictor efficiency of the nephrogenic pressor agents, whatever they may consist of, seems to be somewhat less dependent on vascular cell electrolyte balance than that of the neurogenic catecholamines. This is suggested by the fact that adrenalectomy weakens but does not necessarily abolish experimental renal hypertension^{161, 196, 250, 271, 272} and that renal pathology in Addison patients is accompanied by hypertension in some instances, even without DCA treatment.^{272, 255} How the VEM mechanism and its connection with adrenal cortical function^{253, 272, 275} fits into this picture cannot be evaluated as long as it is not known whether it does or does not act as a systemic pressor agent.

From the point of view of the above outlined concept, the adrenal mineralocorticoids appear as an essential, though not necessarily per se pathogenic link in the origin of essential hypertension, including the neurogenic and renal subgroups. In a minority of cases, they assume a leading role which they are able to keep, however, only under provision that their "biologic material"

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some find " . . . an increased mineralocorticoid excretion²⁷⁹ suggest that adrenal ex-

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it . . . may establish a self-perpetuating form of hypertension which, although initiated by exaggerated mineralocorticoid action, would no longer be accompanied by a demonstrable over-activity of the adrenal cortex.

Role of the Thyroid Gland

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trated by the cases of formerly hypertensive patients who developed Addison's disease^{903b, 7562}. Their blood pressure fell to normal and subnormal levels. It could be restored to within normal range by addition of extra

TABLE 14

Presumable Role of Catecholamines, Mineralocorticoids and Intracellular Sodium (in Vascular Walls) in the Pathogenesis and Treatment of Various Interrelated Forms of Hypertension

TYPE OF HYPERTENSION	POTENTIALLY PATHOGENIC AGENTS	THEIR PRESUMABLE INVOLVEMENT IN THE ORIGIN OF HYPERTENSION	PRESSURE-LOWERING MECHANISMS OF THERAPY
Pheochromocytoma (sustained hypertension)	Catecholamines	Increased	Decreased (excision of tumor)
	Mineralocorticoids	Normal	—
	Sodium (in cells)	Normal	—
Cushing's syndrome	Catecholamines	Normal	—
	Mineralocorticoids	Increased	Decreased (excision of tumor)
	Sodium (in cells)	Increased*	Decreased* (excision of tumor or sodium-poor diet)
Essential hypertension	Catecholamines	Increased?	Decreased (sympathectomy)
	Mineralocorticoids	Increased?	Decreased (adrenalectomy)
	Sodium (in cells)	Increased?	Decreased* (adrenalectomy or sodium-poor diet)

* Conjectural. Concluded from the intracellular Na⁺ increase under the influence of injected DCA

sodium chloride to the diet. However, if, and only if DCA was administered, the blood pressure became again hypertensive

An important role of the local action of ions under the influence of DCA in the maintenance of vascular tone has been postulated already by Swingle and co-workers¹³³⁴ and by Loeb²⁰⁷¹ and was more recently emphasized also by Floyer¹⁰⁰⁹ and by Hajdu and Szent Gyorgyi^{1334a}. This view seems strongly supported by the work of Fleckenstein^{10,0, 1002} on the significance of local electrolyte balance for the electrical membrane potential and contractile power of muscular cells and by the contrasting alterations of

low blood cholesterol level, which one would expect to find in the presence of increased thyroid activity.

All the above-mentioned findings can be accepted as proof of the non-thyrogenic character of the hypermetabolism in essential hypertension.

genic neurohormones (p. 75) for whose exaggerated activity is a fundamental feature of "neurogenic" hypertension various indirect criteria have been adduced on p. 263. It is of interest to note that in a number of

TABLE 15

Highest BMR Readings in Patients with Uncomplicated Hypertension in Whom No Pheochromocytoma Was Suspected or Diagnosed, as Reported by Various Authors

BMR (REFERENCE)	BMR (REFERENCE)
+20% ³¹⁰	+50% ³¹⁴¹
+20% ¹⁰⁰¹	+50% ³¹⁴⁴
+20% ²³⁰⁰	+52% ¹¹⁴
+28% ³¹⁴⁵	+55% ³¹⁰
+31% ¹⁰⁴¹	+55% ³¹⁴⁷
+33% ³¹⁰⁰	+55% ³⁰¹²
+35% ¹²³⁰	+77% ³¹¹
+36% ³⁰⁰⁰	+80% ¹¹¹⁶
+38% ³¹¹²	+82% ³¹¹⁴
+40% ¹⁷³⁶	+84% ³²¹
+41% ¹¹¹⁰	+122% ¹¹⁴⁰

hypermetabolic hypertensive cases, thoracolumbar sympathectomy was followed by a drop of the elevated basal metabolic rates, in some of them unaccompanied by a change of the blood pressure level¹²⁴². These observations seem to give further indirect evidence for an adrenosympathetic

the involvement of probably non-calorigenic renal pressor substances in the hypertensive mechanism of some of the cases, and possibly in part to variations in prevalence of either neurogenic epinephrine or nor-epinephrine, of which the latter is said to be less efficient as a calorigenic neurohormone^{1539 2304}. The degree of simultaneous adrenal cortical over-function as an

is of only little significance for the blood pressure level. Thyrotoxicosis may be associated with a slight to moderate elevation of the systolic blood pressure level, however, in conjunction with a normal or lowered diastolic pressure, thus corresponding to the epinephrine pattern of hemodynamics, in contrast to the nor-epinephrine-like characteristics of essential hypertension with its elevated diastolic pressure levels. Genuine essential hypertension can co-exist with both hyperthyroidism and myxedema but its pathogenic independence of these conditions is documented by its persistence after their successful therapeutic correction.

Closer connections between thyroid function and the pathogenesis of essential hypertension used to be suspected when the belief still prevailed that *alterations of the basal metabolic level* are entirely dependent on thyroid activity. Elevations of the basal metabolic rate are frequently, though by no means regularly, seen in patients with essential hypertension, even without renal or cardiac complications which are apt to further increase oxygen consumption (pp 311 and 501). Some of these hypermetabolic cases show an accelerated heart action, wide pupils, dermal vasomotor instability and accentuated perspiration^{114 1352 1353 2303 2432 3539}, suggestive of thyrotoxicosis. The misleading and awkward term "non-goiterous thyrotoxic hypertension" was quite widely used to set such cases apart as a supposedly thyrogenic subgroup of essential hypertension. The fallacy of this designation became gradually recognized, when discrepancies between the degree of hypermetabolism on the one hand and of heart rate and circulatory velocity on the other²⁵⁵⁹ were pointed out, and when it became clear that thyroidectomy and iodine treatment do not necessarily diminish the high metabolic rates of such cases²³⁵⁹. Morphological examination of the thyroid glands of hypertensive individuals did not reveal any indications of thyroid over-activity^{1552 2359 2452} and iodine metabolism studies in 17 cases of hypertension with hypermetabolism led to the same negative conclusion²¹¹⁴. Furthermore, it was observed that in some hypertensive patients who suffered from actual concomitant hyperthyroidism, as concluded from the histologic appearance of the excised glands and from general clinical improvement after thyroidectomy, the latter was not accompanied by a normalization of the metabolic rate. In others, the basal metabolism was reduced by thyroidectomy³⁵⁴² or radiation treatment¹⁹⁰, but the hypertension remained unchanged. Conversely, relatively high basal metabolic levels were occasionally seen in patients with frank myxedema plus hypertension²³⁴⁹. The blood cholesterol level has been described as being slightly to moderately elevated in the majority of patients with essential hypertension^{110, 3573} and although no unanimity exists on this point³⁵⁷³, there is certainly nothing in the reports of the literature which would suggest a generally

sclerotic ischemia of the brain [central neurogenic hypertension^{193, 2434, 2102} (p. 267 ff.)] and of the kidneys [renal hypertension (p. 278 ff, 313 ff)].

As far as an evaluation of the problematic causal role of hypogonadism in the pathogenesis of essential hypertension from the effects of administered sexual steroids is concerned, no conclusive results have been obtained. An alleged depressor action of testosterone in hypertensive individuals^{197, 227, 237, 2434} was not confirmed^{127, 190}. The effects of estrogens seemed likewise contradictory but with the bulk of the evidence^{249, 252, 247, 252} weighing heavily against claims^{219, 207} of a significant blood pressure lowering effectiveness of ovarian hormones.

Since experimental observations on intact and experimentally hypertensive animals (pp 54 and 55) also failed to yield any impressive results of castration or of treatment with gonadal steroids regarding blood pressure regulation, it appears justified to discount gonadal function as a major factor in the pathogenesis of essential hypertension.

Clinical Differentiation of Pathogenic Types

Attempts to differentiate clinically between the main types of essential hypertension (neurogenic, hormonal, renal) and to analyze their interchangeable coexistence in individual cases, are of more than theoretical importance. An approximate pathogenic identification of a given case may influence both its prognostic evaluation and the decisions to be made regarding the most promising therapeutic procedures.

Prevalingly *neurogenic hypertension* can generally be assumed to exist in patients of the younger age groups in the absence of a history and of clinical signs which would indicate primary renal pathology (glomerulonephritis, pyelitis, etc.) or definite endocrine derangements (Cushing's syndrome, toxemia of pregnancy, hypertensive paroxysms of the pheochromocytoma pattern). A conspicuous lability of the blood pressure level

necessary to obtain more - - - - - , but a detailed examination is

The existence of a pheochromocytoma, by a pheochromocytoma, makes it imperative to consider a pheochromocytoma in every patient with essential hypertension, especially if the blood pressure is radically lowered by a pheochromocytoma.

Various specifically *neurogenic functional reactions* have been suggested

auxiliary calorogenic factor^{1193, 2906, 3412} must also be taken into consideration.

The fact that in older age groups a tendency toward lower metabolic rates becomes conspicuous¹⁰¹ suggests a gradual decrease in thyroid activity which is believed to contribute to the progress of arteriosclerosis (p. 255). It does not seem to interfere with the persistence of hypertension, which can be assumed to shift in these later stages largely from the neurogenic to the nephrogenic pattern.

Role of the Gonads and of Age

An apparent causal connection between the relatively frequent occurrence of a labile and sometimes subsequently stabilizing type of hypertension in menopausal women and the hormonal pattern of the climacteric has been discussed on p. 187. Although the gonadal steroids possess certain vasodilator properties (p. 54 ff.), it was emphasized that the development of hypertension at the age of sexual involution cannot be attributed simply to a loss of this factor but rather to the complex adjustments of pituitary-adrenocortical function to aging, in conjunction with changes in neurohormonal activity. Early castration does not seem to affect the vascular tone²⁵⁰³.

In the male, the decline of gonadal function occurs at a much slower pace (p. 192). Whether or not the gradual increase of the average blood pressure of aging men, as reflected in an extensive statistical study by Russek²⁹⁰⁰, should be considered as an indirect result of gonadal involution is an academic question. The diminishing activity of the sexual glands fits into the general hormonal picture of the aging body, but there is nothing that would suggest its specific significance regarding cardiovascular changes.

It has been pointed out²⁹⁰⁰ that in the older age groups the incidence of hypertensive (above 149 mm) systolic pressures continues steadily to rise (34.4 per cent of the cases over 60 years were found to be hypertensive). The incidence of abnormally high (above 95 mm) diastolic pressure levels mounts until the seventh decade and comes to a standstill from there on. Within the "normal" (less than 150/96 mm) groups, the systolic pressure tends to increase with age, but in contradiction to general belief, the average diastolic level shows a progressive decline, resulting in a frequent occurrence of diastolic levels below 70 mm in old men²⁹⁰⁰. These divergent trends of systolic and diastolic pressures were interpreted as being due to a progressive loss of elasticity of the aorta and large vessels²⁹⁰⁰. On the other hand, the more or less parallel elevations of systolic and diastolic pressure levels among the pathologically hypertensive cases of an advanced age are ascribed to the pressor mechanisms, resulting from progressing arteriolar

of systolic and diastolic blood pressure^{1067, 1071, 2144} which equals that elicited by barbiturates¹⁰⁵⁷. The heart rate and cardiac output are usually augmented by TEA^{1071, 2144}. The blood pressure response to TEA (0.2-0.5 grams i.v. or up to 20 mg/kg i.m.)²¹⁴⁴ has been recommended as a criterion of neurogenic pathogenic mechanisms in essential hypertension^{273, 1071, 1125, 1924, 2144}. Out of a series of 169 hypertensive patients, 143 showed a fall of blood pressure²¹⁴⁴. Among those who did not respond, there were some with manifest renal insufficiency. It is worthy of note that the cold pressor reaction can be abolished by TEA²⁷¹, but the pressor effect of epinephrine is not counteracted^{267, 2144}. The marked daily variations of both the depressor responses to serial injections of TEA and of the blood pressure floors in some hypertensive patients, suggest a fluctuating interaction of neurogenic and humoral (renal?) mechanisms in these cases¹⁹²⁴. Among those numerous

TABLE 16

Average Blood Pressure Responses in Thirty Cases of Essential Hypertension (After R. Gubner, F. Silverstone and H. E. Ungerleider, J.A.M.A. 130:325, 1946¹¹⁴⁴)

TYPES OF TESTS	INITIAL BLOOD PRESSURE LEVELS (AVERAGES)	AVERAGE CHANGES FROM INITIAL READINGS	
		systolic	diastolic
		mm Hg	mm Hg
Breath holding	181/110	+27	+23
Cold pressor test	187/112	+24	+18
Hyperventilation	187/114	-16	-11
Carotid pressure	190/116	-21	-15
Hyperventilation plus carotid pressure	187/113	-30	-19
Sodium amytal	189/114	-33	-17

hypertensive individuals in whom a depressor effect of TEA occurs, those with a marked diminution of systolic pressure and pulse pressure (the latter due to a relative refractoriness of diastolic levels) and with little or no increase of heart rate were considered as having advanced arteriosclerotic changes¹⁰⁷⁷. Occasional side effects of intravenously injected TEA consist of weakness, light-headedness, postural hypotension and even circulatory collapse. Intramuscular administration may be distressing through nausea, loss of visual accommodation, a dry mouth and temporary inability to void and defecate²¹⁴⁴. Recent studies of the reaction of hypertensive patients to pentamethonium and hexamethonium salts^{22, 2010, 2144} and other compounds¹⁹²⁴ whose ganglionic blocking action resembles that of TEA²¹⁴⁰ revealed a similar depressant effectiveness.

The most direct information regarding adreno-sympathogenic neurohormonal activity in essential hypertension might be expected theoretically from the response to specific "adrenolytic" and "sympatholytic" drugs, such

for clinical use in patients with essential hypertension, such as an increased pressor response to CO_2 inhalation, to breath-holding, to cooling of one hand in ice water, to the upright position, to physical exercise, to pain stimuli, and to inhalation of ammonia; furthermore, increased depressor effects of hyperventilation, barbiturates, acetyl-beta-methylcholine and carotid sinus pressure (p. 264 ff.). However, none of these reactions is sufficiently dependable and sufficiently well standardized to serve as a suitable criterion by itself. More meaningful results may be obtained by combining and correlating several such tests, as proposed by Gubner and co-workers¹³¹⁴, who outlined the following procedure: (1) At the end of a normal expiration, the subject is instructed to stop breathing without straining. After 20 seconds of apnea, the highest systolic pressure is recorded. The subject is then permitted to breathe normally for a few moments and the test is again repeated, this time the highest diastolic level being recorded after 20 seconds of apnea. (2) A piece of gauze, saturated with aromatic ammonia, is held over the nose and the blood pressure (systolic and diastolic) is determined during brief inhalations of the irritant. (3) The subject is instructed to breathe maximally with deep inhalations and exhalations at a slightly rapid rate, without effort or straining. The systolic blood pressure is recorded after 30–60 seconds of hyperventilation. After a short resting period, hyperventilation is repeated, this time for measurement of the diastolic pressure. With the patient still breathing deeply, digital pressure is applied over the carotid sinus, preferably the left, and the lowest systolic blood pressure attained during the next half minute is recorded. This is followed by measurement of the diastolic pressure under analogous conditions. All readings should be made on the same arm. Results obtained by Gubner and co-workers¹³¹⁴ with this method in 30 cases of essential hypertension and including also those of cold pressor and sodium amytal tests are represented in Table 16. In normal persons, the average cold pressor reaction is plus 12/10 mm in the sitting position¹³¹¹. For patients with essential hypertension, grouped according to different degrees, the corresponding average values were plus 34/25 and plus 47/34 mm respectively. In the recumbent position, the reactions were found about 50 per cent smaller¹³¹⁷. An excessive cold pressor reaction was observed three times as frequently in hypertensive individuals as in normotensives and an exaggerated response to the upright position twice as frequently as in normotensives¹³¹³.

Symptoms of the "hypertensive diencephalic syndrome" can be provoked in susceptible persons by intradermal injection of histamine¹⁰⁴¹

The selective blocking action of tetraethylammonium (TEA)³ on autonomic ganglia causes only insignificant depressor effects in normotensive humans^{2027, 2114}, but in hypertensive patients it produces a considerable fall

2481 2479 2451 After intravenous application of 0.3 mg, the blood pressure falls an average $24/8$ mm within 25 minutes in hypertensives, as compared with $7/2$ mm in normotensive individuals¹⁷⁰¹. The peripheral resistance is usually 299 1701 decreased and the cardiac output augmented¹⁷⁰¹, except in cases of "minute volume hypertension" which show opposite reactions^{299, 2451}. The depressor action of CCK-179 and of the individual dihydrogenated ergot alkaloids is demonstrable with greatest regularity (about 80 per cent) in patients with uncomplicated, supposedly neurogenic, essential hypertension, but it was also observed in about 50 per cent of persons with "renal" hypertension, indeed, in some of the latter whose pressure levels were very high, it occurred with exceptional intensity (average $-38/13$ mm)¹⁷⁰¹. The reason for this behavior may be sought in a possible interference with a neurogenic mechanism, superimposed in such patients on a nephrogenic hypertensive pressure floor. However, as long as nothing definite is known regarding the effect of CCK-179 and of related compounds on strictly renal humoral pressor reactions, it is not possible to draw any far-reaching conclusions from ergot alkaloid tests concerning the participation of neurogenic or renal factors in essential hypertension¹⁷⁰¹.

A prolonged lowering of the blood pressure was reported after intravenous administration of 5 mg/kg of dibenamine hydrochloride in cases of "benign or moderately advanced essential hypertension", but not in patients with malignant hypertension according to one team of workers¹⁷²⁰ while others¹⁴¹⁴ found this drug efficient also in cases presenting the latter syndrome.

All in all, the recognition of neurogenic mechanisms, operating in a given case of hypertension, is possible by evaluation of the history, observation of the spontaneous fluctuations of the blood pressure, combined application of certain functional tests (breath-holding, hyperventilation, carotid sinus compression, cold stimulus, inhalation of ammonia) and of sedatives (barbiturates), ganglionic blocking (TEA) and adreno-sympatholytic drugs (CCK-179, dibenamine). Neither a correct quantitative estimation of co-existing humoral non-neurogenic mechanisms, nor even definite information regarding their presence or absence can be expected as a rule from the tests described in this section. Only if humoral pressor factors are overwhelmingly active may they prevent a positive result of the "nerve" tests and justify the suspicion of a preponderantly renal mechanism, in conjunction with other clinical criteria of renal involvement.

In abnormally increased pituitary-adrenocortical activity as the prevalently responsible pathogenic factor in the individual case...

as the ergot alkaloids, benzodioxanes, imidazolines and β -haloalkylamines. Yet, it must be borne in mind that these drugs interfere mainly with the actions of circulating catecholamines ("adrenolytic" effect), while larger doses than practicable in clinical cases would be required to completely suppress the effects of the locally discharged sympathogenic neurohormones in their respective effector cells ("sympatholytic" dosage). The benzodioxane and regitine tests for pheochromocytoma are based on the principle of "adrenolytic" but not "sympatholytic" dosage.

The mechanisms of action of the adrenergic blocking agents differ in various respects. The ergot alkaloids e.g. depress the central transmission of vasomotor reflexes through the brain stem^{111, 1379} beside their peripheral adrenergic blocking effect and, with the exception of their dihydrogenated derivatives (DHE-45, DHK-135, DHO-180, CCK-179)¹³⁷³, they exert disturbing directly stimulating effects upon the smooth muscles. This latter property they have in common with the imidazolines and benzodioxanes (lit., see ¹⁴⁴, also ¹⁴¹). The finer mode of action of the adrenergic blocking drugs is still obscure, but it is believed that they do not affect either the molecular structure of the adrenosympathetic catecholamines, nor the cell permeability for these agents¹⁴⁴. Since they invert the blood pressure effect of epinephrine (apparently by leaving its vasodilator component intact¹⁴⁵) but only weaken the purely vasoconstrictor effect of nor-epinephrine, it can be understood that combined and overlapping reactions may result from their administration, in accordance with the mutual proportions of circulating and of intracellularly acting epinephrine and nor-epinephrine. All of these complications tend to confuse the issue and to limit the informative value of the drugs in question in the diagnostic evaluation of neurohormonal hypertensive mechanisms.

The cold pressor reaction can be diminished by dibenamine¹⁴²⁹ or by dihydrogenated ergot alkaloids^{1084, 1701}, but it was not found significantly altered by benzodioxane¹⁴².

As earlier discussed in connection with the differential diagnosis of pheochromocytoma, the benzodioxanes lower the hypertensive blood pressure only if it is due wholly or in part to circulating catecholamines. Contrarywise, they leave the pressure of ordinary hypertensive cases unchanged or even raise it¹⁴⁵ by virtue of their musculotropic side action. They are of no particular usefulness for the identification of neurogenic mechanisms.

Ambiguities of a different nature impair the diagnostic value of tests performed with the dihydrogenated ergot alkaloids in that their depressant effects are composed of central nervous reflex inhibition and peripheral adrenergic blocking action¹⁴⁵⁵. CCK-179 ("hydergin"), a preparation combined of dihydroergocornine, dihydroergocryptine and dihydroergokryptine, offers the advantage of a practically undisturbed depressor effect^{139, 1701}.

drawal or by elimination of the intracellularly sodium-depositing adrenal mineralocorticoids (subtotal or total adrenalectomy).

Psychotherapy by itself will not abolish an established chronic hypertension, but it can do much to improve the patient's subjective well-being and to reduce further hypothalamic-sympathetic-adrenocortical extra stimula-

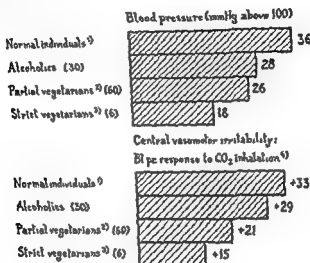


FIG. 40. Apparent effect of dietary habits on blood pressure.

(3) Persons, having refrained from all kinds of animal food stuffs, including dairy products, for an average period of 4 years.

(4) The CO₂ standard stimulus was applied to 10 men, 1 min.

tions.^{1941, 2015, 2027} It may be supported by the occasional use of sedatives²⁰¹ which are not to be recommended for prolonged treatment²⁰¹, however. Undue concentration of the patient's mind on his blood pressure level (Fig. 41) is apt to cause an anxiety complex and to further aggravate his condition.

Surgical excision of parts of the visceral sympathetic neurosecretory apparatus was first performed by Brunning (1923)²⁰² as a therapeutic procedure for hypertensive crises. It was introduced into the United States by Rowntree and Adson in 1925²⁰³ and perfected to greatest efficiency on a large scale

indirect hormone assay. The epinephrine-eosinopenia test²²¹ may indicate an exaggerated pituitary secretory responsiveness unless the absolute eosinophil count is abnormally low from the beginning due to increased glucocorticoid secretion. The sodium determination in thermal sweat^{65, 849, 2067} serves as a criterion of mineralocorticoid activity. Procedures of fractionated hormone assay are still in their infancy, but they hold promises for future clarification of the hormonal forces involved in the origin of those variegated combinations of pressor mechanisms, which are still pooled under the collective and non-committal term "essential hypertension".

Prevention and Treatment

A discussion of possibly preventive measures which might have some bearing on the neurohormonal and hormonal factors involved in essential hypertension must be of a rather academic character; e.g., consideration of the hereditary tendencies of hypertension^{102, 1981, 3534} before entering matrimony, restriction of animal fats and lipids in the diet as potential precursors of excess cortical steroids, avoidance of mental conflicts and abnormally stressful situations, as initiators of the hypothalamic-adreno-medullary-pituitary-adrenocortical chain of reactions, and abstinence from nicotine as an adrenosympathetic stimulant.

Certain observations, such as the low incidence of hypertension among strictly vegetarian monks²⁹¹³ and the temporary diminution of the blood pressure level of hypertensive persons on a starvation diet^{399, 2109}, would seem to justify a systematic investigation of the cardiovascular status of religious groups and of organized faddists who adhere to exceptional dietary principles and living habits in the midst of a racially comparable population. The writer has carried out studies of this kind on 60 members of vegetarian societies²⁴⁹². They revealed a relatively low blood pressure level and low central vasomotor irritability in these individuals, but the statistical significance of the findings remains open to question (Fig 40).

In contrast to Utopian recommendations for prophylaxis, the actual treatment of existing hypertension can be viewed more realistically, regarding both its aims and its result. In keeping with the pathogenic concepts outlined on pp 263-289, the following therapeutic approaches appear rational and have already yielded tangible results: a) interference with assumed exaggerated adrenosympathetic neurosecretory pressor activity by diminution of central stimuli (psychotherapy, rest, sedation), interruption of neurosecretory pathways (sympathectomy, ganglionic blockade) and pharmacodynamic counteraction against neurohormonal pressor effectiveness (anti-adrenergic and vagotropic drugs), b) interference with the electrophysical prerequisites of vascular contractile responsiveness to the ever-present intrinsic neurohormonal pressor catecholamines by sodium with-

drawal or by elimination of the intracellularly sodium-depositing adrenal mineralocorticoids (subtotal or total adrenalectomy).

Psychotherapy by itself will not abolish an established chronic hypertension, but it can do much to improve the patient's subjective well-being and to reduce further hypothalamic-sympathetic-adrenocortical extra stimula-

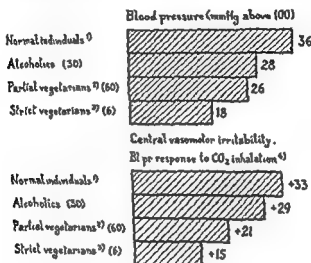


FIG. 40. *Essential hypertension*.

tions^{1943 2505 2537} It may be supported by the occasional use of sedatives²⁵¹ which are not to be recommended for prolonged treatment²⁰⁴, however. Indue concentration of the patient's mind on his blood pressure level (Fig. 41) is apt to cause an anxiety complex and to further aggravate his condition

Surgical excision of parts of the visceral sympathetic neurosecretory apparatus was first performed by Bruning (1923)²⁰⁰ as a thera-

by Peet²⁴² (supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy), Smithwick^{277, 279} (dorsolumbar sympathectomy from the eighth or ninth thoracic ganglion to the second lumbar ganglion, including the splanchnic nerves) and Grimson (total paravertebral sympathectomy)¹²⁴.

It would transgress the scope of this review to evaluate the merits and shortcomings of the different techniques used, but it might be mentioned

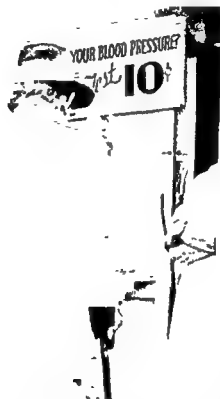


FIG 41 Anxiety for sale (1939) (Photograph by W. Raab)

that the less radical methods were criticized by Goetz¹⁶² as permitting a re-organization of severed nervous connections and thus as not offering the maximum of lasting benefit.

Taking the resting blood pressure level as criterion of therapeutic effectiveness, Smithwick²⁷⁷ recorded in a large series of cases an average diminution of 61/43 mm (systolic/diastolic) in 41 per cent of the operated patients, of 44/24 mm in 20.5 per cent and of 27/15 mm in 17.9 per cent; in other words, a considerable improvement in 79.4 per cent. Comparing 125 sympathectomized cases with 50 comparable non-operated hypertensive individuals, he²⁷⁹ reported 42.3 per cent versus 10 per cent as improved, and 8.9 per cent versus 50 per cent as worsened within a period of five

years. Out of 108 patients operated by Grimson¹²⁹², 25 had a normal and 44 a diminished hypertensive pressure six months to eight years after the operation. According to Hammarström¹²⁹⁷, the blood pressure was significantly reduced six months to six and a half years after operation in about one-half of all cases sympathectomized by Swedish surgeons. In a series of 338 cases, splanchnicectomy was followed by a significant reduction of the diastolic pressure (20 mm or more) in 29 per cent¹²⁴⁴.

Such favorable reports were partly contradicted by a critical survey¹²⁰ of 100 sympathectomized patients of whom only 8 per cent presented a normal blood pressure and only 13 per cent a significant pressure reduction within a still hypertensive range five years after surgical intervention. These discrepancies were ascribed to a probable involvement of psychological factors, affecting the cardiovascular tone during the blood pressure measurements before and after sympathectomy¹⁰³.

More important than the effect upon the resting blood pressure is perhaps the dampening influence of sympathetic surgery upon superimposed pre- or reflexes^{1267 1625}, although this too may fail to appear, especially regarding emotional hypothalamic stimuli¹²⁰ (encephalin action?). A prolongation of life for periods of years as the crucial test for the value of sympathectomy seems to be well established from several statistical studies^{1245 1252 2140}, based on comparison with classified longevity data of medically treated patients^{100 174}. Remarkable improvements of vascular ocular lesions, such

... subjects are suitable for sympathectomy and rules for admission to operation have been worked out by several surgeons^{124 127 191 1297 2122}. They differ in various details but include the following essential points which proved useful in the selection of patients for worth-while results: a progressively rising diastolic pressure near or above 130 mm; retinal hemorrhages and exudates, cerebral vascular episodes without persistent symptoms, signs of cardiac failure which respond satisfactorily to medication, a family history of early deaths from hypertensive vascular disease; age below 50-55 years. Contrariwise, sympathectomy is contra-indicated in the presence of marked excretory insufficiency of the kidneys, as indicated by an elevated NPN and a low phenolsulphonephthalein excretion (less than 15 per cent in the first 15 minutes and less than 50 per cent within two hours), advanced encephalopathy, severe arteriosclerosis of the retinal vessels and uncontrollable congestive heart failure. ...

lumbar technique is used¹²³. However, the mortality among such patients is relatively great¹¹².

A variety of functional tests was studied specifically concerning their possible value as auxiliary criteria for prognostic estimation of the potential effectiveness of sympathectomy. A definitely lowering effect of amytal upon the diastolic pressure level was considered a fairly useful guide by some observers^{31, 181, 217}, at least insofar as its absence seemed to preclude a satisfactory result of sympathetic surgery. Others, however, found the amytal test and the reaction to nitrites so frequently misleading^{1257, 518} that not much practical information can be expected from these methods. The same has to be said concerning the cold pressor reaction¹²⁵⁷, caudal anesthesia¹²¹⁶, the application of CCK-179 and other ergot alkaloids¹⁷⁰¹, tetraethylammonium^{1212, 2113}, priscol and dibenamine¹²³². Even the spontaneous fluctuations of the blood pressure under ordinary environmental influences, which may exceed those evoked by specific tests^{106, 1232}, cannot be relied upon as presaging success or failure of sympathectomy.

These experiences, as well as the paradoxical fact that sympathectomy occasionally fails to achieve complete normalization in a seemingly pure neurogenic case⁷³⁰ while causing distinct improvement in some patients with renal pathology^{730, 1257, 2175}, are difficult to explain. It may be mentioned in this connection that even in totally sympathectomized animals, vigorous centrogenic vasoconstrictor reflexes were seen to persist^{112, 1050, 1239}, a phenomenon in which cerebral neurosecretory discharges of enkephalin have been suspected to participate²⁶³⁴. In sympathectomized patients the continued presence of a certain degree of sympathetic tone of the peripheral vessels could likewise be demonstrated²³⁰⁶. On the other hand, severe but reparable functional damage of the kidneys can be produced by an excess of circulating adrenosympathetic neurohormones, as in cases of pheochromocytoma (p. 83 ff.).

It seems worthy of note that in sympathectomized patients the urinary excretion of sympathomimetic catecholamines proved distinctly decreased^{1141, 2696} and that in totally sympathectomized animals, the concentration of such amines in the denervated tissues was likewise found by the writer and the late J. P. Maes²⁷¹⁴ to be markedly diminished.

Untoward side effects of the extensive forms of sympathectomy, such as neuralgic pains which may continue for months, impairment of ejaculation, and orthostatic hypotension, may be annoying but are in most instances preferable to the preoperative state of affairs and its long-range potentialities. The decision as to whether or not to operate must ultimately rest with the surgeon, probably somewhere in the middle of the road between the restrained indication for only 4 per cent of the patients with essential hypertension⁹⁹¹ and the liberal recommendation of sympathectomy for all

young individuals with a pressure level from 140/90 mm up¹²². A new surgical approach of hypertension, the intramedullary transection of vaso-motor tracts¹²³, has been tried in a few cases with seemingly promising results and may deserve more extensive study.

The advent of *adrenosympatholytic* drugs with a minimum of disturbing musculotropic action but with a central nervous component, notably dihydroergotamine (DHO-180) and hydergin (CCK-179), appears to offer a partial substitute for surgical interference. Encouraging, though by no means dramatic therapeutic results^{1701, 1702, 1703, 1704, 1705, 1706} have been reported, such as an average fall of the resting blood pressure levels of 38/10 mm¹⁷⁰¹ and a prevention of superimposed pressor reactions¹⁷⁰³ and pressure crises¹⁷⁰¹. The oral intake of hydergin (0.3-1.5 mg once to three times daily) or its parenteral administration (0.1-0.6 mg daily or every other day), or a combination of both, are said to depress the blood pressure only after two or more weeks¹⁷⁰³, but to produce prolonged after-effects after two or three months of continuous treatment. Permanent medication with intervals may be given when necessary and if tolerated. Nausea, dizziness and diarrhea were observed in about 5 per cent of the cases¹⁷⁰¹. Whether or not these drugs will establish a firm place for themselves in the therapeutic armamentarium for essential hypertension remains to be seen. The fact that the dihydrogenated ergot alkaloids are not capable of regularly diminishing the pressor effect of infused epinephrine and nor-epinephrine in humans^{1707, 1708, 1709, 1710} indicates the limitations of their therapeutic effectiveness.

Impressive blood pressure reductions have been recently reported with the use of ganglionic blocking penta- and hexamethonium salts^{121, 1210, 1211, 1212}. One of them (hexamethonium chloride, "methium") is available in oral tablets (250 mg). In hospitalized patients, medication is begun with one tablet four times per day and the dose is gradually augmented to 2 or 3 grams per day. Amounts as high as 5 grams per day may increase the depressor effect but — such as prostrating. Especially in patients with a history of coronary sclerosis, complications may arise from ischemia of the brain and heart muscle. Prolonged treatment with the drugs in question is capable of ameliorating retinal and electrocardiographic changes¹²¹². The need of constant close supervision of the patients and of repeated adjustments of the dosage makes a routine clinical application over long periods of time rather difficult.

Other — — —
have

most potent and most lastingly effective of all adreno-sympatholytic drugs, is too troublesome for routine medical application^{1429, 2329, 3655}; but it is to be expected that less toxic related compounds, such as 6SSA, will prove to be of greater clinical usefulness^{1220a} even though the latter drug was not found impressively effective in one small series of cases^{558a}.

Veratrum viride and its derivatives which lower the blood pressure via vagal reflex pathways^{1537, 2230}, partly by diminishing the cardiac output⁷⁴¹, produced favorable results in about 50 per cent of hypertensive patients, as far as the blood pressure levels and some of the subjective symptoms are concerned^{144, 3624, 3627}. Unfortunately, unpleasant side effects, such as nausea, vomiting, burning sensations in the throat and epigastrium, dizziness, paresthesias and weakness, are common and often prohibit a prolonged administration of the *veratrum viride* drugs. The effective daily dose ranges between 6.0 and 18.0 mg by mouth and requires extremely watchful individual adjustment³⁶²⁴. Sometimes the effectiveness of the medication diminishes after months of treatment. Whether the vagal mechanism involved in the *veratrum viride* effects counteracts the detrimental metabolic influences of the adreno-sympathogenic catecholamines on the cardiovascular tissue would have to be elucidated.

A temporary lowering of hypertensive blood pressure levels has been achieved by the administration of certain *sulphydryl compounds*, such as β -mercaptopropionic acid which antagonize the hypertensive effects of various natural pressor agents (nor-epinephrine, epinephrine, angiotonin, pherentasin)^{1040a}. Their therapeutic applicability is being investigated.

A new drug with renal^{2751b} and cerebral^{1223a} vasodilator action and with limited adrenolytic^{1032a, 1252a, 1309a} properties, *L-hydrazinophthalazine* (*Apresoline*) proved moderately effective in cases of essential hypertension^{1042a, 2404a, 3040b}. In an oral dosage of 75-1400 mg per day, it produced a lowering of both systolic and diastolic blood pressure levels, often accompanied by headaches and postural hypotension. Because of the hazards of the latter for coronary and renal blood supply it has been warned against^{1736a}.

Rigid salt restriction in the diet was first advocated by Ambard (1904)⁴⁴, Volhard³⁷⁸, Allen^{23, 25} and others, and revived with remarkable organizatory energy by Kempner in 1944¹⁷⁴². It is being discussed here as a measure with indirect hormonal implications, insofar as it seems to act by depriving

cooperative pressure-raising effects upon the contractile elements of cardiovascular system (p. 25, Fig. 39). The earlier recommendations of

salt restriction were based mainly on empirical observation. Kempner's rice-fruit regime excludes, besides sodium chloride, also proteins and fats in order to protect the supposedly damaged kidneys against a supposedly excessive functional load. Factors of the latter kind, ill defined as they are, may play a certain secondary role in those cases in which renal damage can be reasonably assumed. However, it seems to the writer in agreement with others^{117 767 1797 2051 2114 2021} who achieved similar results with more liberal but equally salt-poor diets, that deprivation of sodium constitutes by far the most important blood pressure-lowering feature even of the orthodox rice-fruit diet. Statements regarding adrenal corticoid elaboration during salt withdrawal are ambiguous^{171 2196}. The pressor effects of both DCA and of the sympathomimetic catecholamines are markedly weakened, in part even entirely abolished¹⁷⁶⁷. No clear relationship was found between the decrease of the plasma volume, occurring during intake of the rice diet, and the clinical results¹⁹¹⁶.

As far as the latter are concerned, the figures given regarding the behavior of the blood pressure level vary widely. Kempner¹⁷¹² reported 62.2 per cent improvements among 500 patients treated by himself. Other observers whose data are based on much smaller series of cases, partly treated with the strict rice diet, partly with other salt-poor diets, containing less than 0.4 grams of sodium per day, describe a significant reduction of the blood pressure level in 77-83 per cent^{201 767}, 60 per cent^{117, 1098, 1701 2164}, 40-50 per cent^{172 760 1040} and 20-35 per cent^{117 1296 1718 2055 2170} respectively, or deny a beneficial effect altogether¹¹⁰.

Even though some of the impressive results achieved by Kempner¹⁷¹² were ascribed by various critics^{504 2021} to the "evangelical fervor"¹⁹¹¹ of his personal therapeutic approach, and thus to partially psychological effects there is still a

regimen

a sub-

According to Kempner¹⁷¹², 32 per cent of the 311 patients who responded to the rice-fruit diet showed signs of improvement within the 35 first days of the regime, in the remaining 68 per cent, the times of onset were scattered between the 35th and 898th day. In 125 out of the total of 500 patients treated, the blood pressure fell to levels below 145/95 from an average of 191/107 mm.

Unfortunately, the cruel monotony of the rice-fruit diet demands a measure of fortitude which only few patients are capable of maintaining after having been discharged from the discipline of the hospital, and any infringement on the required restriction of sodium intake (0.4 mg or less per day) is likely to offset within a short period of time most of what has been gained¹⁹¹⁴. The strict rice-fruit diet is, therefore, considered as impractical

for sustained treatment, even by those who have otherwise fully confirmed Kempner's statements regarding its efficacy³⁵¹. Since it was also criticized because of its deficiency in nitrogen^{421, 3059}, other more flexible dietary schemes with a low sodium content have been suggested and found effective^{222, 417, 1297, 1735}, e.g., 70 grams of proteins, 80-175 grams of fat, 130-230 grams of carbohydrates, 3 liters of water (including fruit juices), vitamins, and only 0.2 grams of sodium⁴¹⁷. However, the preparation of such diets is fraught with the disadvantage of technical difficulties to keep the sodium content within the prescribed limits. Sodium-free salt substitutes (Neocurtasal, Diasal) and proteins (Lonalac) may be used and sodium depletion can be increased by the administration of ammonium chloride⁷⁶⁷ or of cation exchange resins^{740, 2122}. The latter, if taken in large doses, permit even a daily sodium ingestion of up to 1500 mg without impairment of the clinical results^{1277a}.

Under all circumstances, a constant supervision of the patients living under a low salt regime is necessary for several reasons. In the first place, the patient's adherence to the rules laid down for him must be frequently checked by analysis of the urine for sodium excretion^{1735, 1943, 3034}. Secondly, it must be kept in mind that serious sodium depletion, leading to hyponatremia, weakness, oliguria, acidosis, azotemia, vascular collapse and even death^{504, 767, 1297, 2159, 3034, 3197} may occur, especially in patients with advanced renal pathology^{2167, 2477, 3034}. Abnormally low serum sodium levels serve as a warning signal and require the administration of adequate amounts of sodium chloride, if necessary by the venous route, to replace the calculated losses^{1297, 2167, 2775, 3036} (see Relman's formula, p. 510).

No hard and fast principles regarding the indications for a practically sodium-free diet in essential hypertension have yet been, nor probably ever will be developed, as the degree of the patient's psychological and financial ability to cooperate will always introduce a major element of uncertainty into the situation. Even the most successful application of a salt-poor diet can hardly be considered as an equivalent substitute for sympathectomy in a patient otherwise suited for operation, unless it is carried out for an unlimited length of time. On the other hand, it may prove at least temporarily useful in the management of patients who have been declared poor risks for surgery. Particular benefits to be derived from salt restriction in the presence of cardiac complications will be discussed on p. 509 ff. The frequently observed striking improvements of the patient's renal and ocular status^{1743, 1755, 3514} must be considered as important additional advantages, regardless of the response of the blood pressure.

The reasons for failure of salt-poor diets to lower the hypertensive pressure in many instances are unknown. It is interesting to note that salt

withdrawal proved dramatically effective in about 60 per cent of a series of unsuccessfully sympathectomized hypertensive patients²¹¹. From the point of view of the hypothesis concerning the role of the electrolytes in cardiovascular contractility (p 25), it seems possible that sodium withdrawal per se may not suffice to suppress the hypertension-producing adreno-sympathogenic neurohormonal and nephrogenic humoral pressor stimuli if they have attained a certain magnitude and if a continued mineralocorticoid production tends to stubbornly retain the sodium reserves within the contractile cells. Besides, it is apparently not the intra-extracellular distribution of sodium alone which determines the

monal therapeutic measures, aimed at the electrolyte situation, will depend ultimately on this latter factor. The profoundly depressant influence of potassium deprivation on the blood pressure level and on the pressor efficacy of DCA^{1039, 1062, 1063} has not yet been systematically explored regarding its conceivable therapeutic potentialities.

Artificial reduction of adrenal cortical function has been achieved by unilateral or by subtotal or total bilateral adrenalectomy^{702, 704, 903, 1093, 1232, 1644, 2170, 2299, 2400, 2464, 2720} with strikingly beneficial results in Cushing's syndrome^{1741, 1881} and in malignant hypertension^{1232, 1441}. Although a similar effectiveness might be anticipated theoretically in any case of essential hypertension, this form of treatment cannot be considered as the general method of choice for obvious reasons. More will be said about adrenalectomy on p 318 ff.

Röntgen irradiation of the adrenal region did not exert any appreciable effect upon the blood pressure in the writer's experience²⁴⁴, but combined X-ray treatment of the pituitary and adrenal glands was described as having lowered the systolic and diastolic blood pressure level by an average of 30 to 40 mm respectively in more than 200 patients^{1415, 1416}. Irradiation of the pituitary alone was likewise reported to have

Other observers found this treatment effective in only one out of four cases^{2557, 2559, 2562}.

The claims and emphatic counter-claims concerning the therapeutic value of gonadal steroid preparations in essential hypertension have been mentioned on p 293.

Summary

The term "essential" hypertension includes three often coexisting and overlapping categories of pressor mechanisms which result in elevations of the systolic and diastolic pressure levels. Available experimental and clinical evidence suggests the existence of the following pathogenic factors in a more or less hypothetical fashion:

(1) *Exaggerated neurosecretory liberation of adrenosympathogenic catecholamines, chiefly nor-epinephrine*, for the most part by direct discharge into the contractile cells of the cardiovascular system, and therefore not detectable in the blood. The higher level stimuli for these exaggerated peripheral neurosecretory effects can originate (a) in the carotid sinus and other pressoreceptor areas (weakening of depressant vagal reflex stimuli due to reduced distensibility of the arterial wall and resulting sympathetic pressor preponderance), (b) in the cerebral cortex and subcortical ganglia (psychogenic hypertension) and (c) in the cerebral vasoconstrictor "center" areas (increased excitability due to arteriolar sclerotic cerebral-medullary ischemia and local hypoxic acidification). These primary neurogenic mechanisms seem to be prevailingly responsible for the earlier stages of essential hypertension in a large number of cases, as suggested by various functional tests which disclose increased sympathetic tone and central vasomotor excitability.

(2) *Exaggerated adrenocortical activity*, involving either an absolute or a relative preponderance of mineralocorticoids, possibly initiated by neurohormonal-hypothalamic-pituitary stimulation (alarm reactions) and producing augmented intracellular deposition of sodium in the arterial walls. The resulting alteration of the electrical cell membrane potential causes the vascular muscle cells to respond to either normal or increased amounts of intrinsic depolarizing adreno-sympathogenic neurohormones with exaggerated pressure-raising contractions. Positive evidence for an absolutely increased adrenocortical activity was obtained only in a minority of cases with essential hypertension, but an at least normal cortical function and a certain minimum of intracellularly retained sodium seem to be necessary to permit an effective pressor activity of adrenergic (and renal?) pressor agents.

(3) *Chemically unidentified humoral pressor substances* (VEM?, pherentasin?) originate in the kidneys if their blood flow is reduced either temporarily by neurogenic vasoconstriction or permanently by arteriolar sclerotic changes. There is reason to suspect that the latter may be caused or aggravated by a noxious local metabolic influence of the constricting adreno-sympathogenic catecholamines which constantly pass through the renal arterioles. Thus, the common renal lesions, occurring in essential hypertension and further aggravating it, may likewise be regarded hypothetically as a result of toxic adrenosympathogenic neurohormonal action.

The rationales of all partially or completely successful therapeutic measures known so far, as well as the reasons for their failures, are tentatively deductable from the above-outlined pathogenic concepts in which the integrated functional correlations between the adrenosympathogenic pressor neurohormones with the adrenal mineralocorticoids, and the influence of the latter on intra-extracellular electrolyte distribution (total electrolyte gradient) occupy a dominating position: (a) psychotherapy, ganglionic blocking agents and sympatholytic drugs diminish adrenosympathogenic neurosecretory pressor effectiveness functionally, (b) sympathectomy, surgically; (c) salt withdrawal or artificially hypoadrenocortical sodium depletion, by weakening vascular contractile responsiveness to neurohormonal stimuli. Renal humoral pressor agents and possibly cerebral vasopressor neurosecretion (encephalin?) may interfere with or entirely prevent the therapeutic efficacy of these measures.

“Malignant” Hypertension

Definition and General Principles

The term “malignant” hypertension was introduced in Germany by Volhard and Fahr (1914)²⁴³³ and in the United States by Keith, Wagener and Kernohan (1928)¹⁷³⁵ for a syndrome which, although differing from “essential” hypertension in several respects, has much in common with it pathogenically and symptomatically. Indeed, some authors feel inclined to regard “malignant” hypertension merely as a variety of essential hypertension, distinguished by quantitative exaggeration of certain features rather than as a qualitative morbid entity. Accordingly, the term “malignant phase” of hypertension³³³ is not infrequently employed.

Apart from high and rather stable levels of the systolic and diastolic blood pressure (the latter usually higher than 120 mm)¹⁷³⁵, the most characteristic clinical sign of “malignant” hypertension is the presence of marked retinal changes, consisting of papilledema, exudates and hemorrhages. These ocular manifestations are but the directly visible exponent of a severe generalized diffuse arteriolitis with hypertrophy, hyalinization and necrosis of the media, and abundant intimal proliferation^{1735, 3509, 3451}. These vascular lesions are comparatively evenly distributed throughout the entire arteriolar system and in the advanced stages they are accompanied by functional disturbances of the brain, the heart and the kidneys^{724, 1735, 2464, 2474, 3451}. Intense headaches²⁴⁷⁴ constitute a common and early symptom. Loss of weight and malaise occur in many cases, but usually without anemia; the latter in contrast to conditions in chronic glomerulonephritis¹⁷³⁵.

Males are afflicted about twice as frequently as females (37 per cent vs. 17 per cent of a large series of hypertensive individuals)¹³⁵⁷. The age of onset is a relatively early one (72 per cent between 20 and 49 years) and progression to death is inexorably rapid in untreated cases. Among 81 patients of one series¹⁷³⁵, 91 per cent died within 51 months (the majority within two years) after the diagnosis had been made and only five lived two years longer; the average length of life after diagnosis was eight months. It was said that the course is the speedier, the younger the patient¹⁴⁹¹. In some cases, the condition is not preceded by any recognized pathological state; others may have displayed what appeared to be “benign” essential hypertension for periods as long as nine years before the onset of “malignant” symptoms¹⁷³⁵.

Contrary to earlier beliefs^{990, 1457, 1735, 2179}, death does not always result from kidney insufficiency and uremia. In fact, renal lesions of a major

degree may be entirely absent at necropsy^{724, 1659, 2474}. Most of the patients who do not succumb to uremia die from congestive heart failure or from cerebral accidents. Thus, the causes of death are in principle the same as in essential hypertension, but with a much higher incidence of renal complications. In some instances, death from uremia occurred in the absence of demonstrable necrotizing vascular lesions in the kidneys^{657, 1725, 2464}.

The peripheral resistance was found increased⁷⁹⁴² with a subnormal cardiac output as long as kidney function remained adequate¹⁴²⁰, but it decreased in the cases examined when renal failure set in, and the cardiac output became augmented. The basal metabolism was reported as being between plus 10 per cent and plus 20 per cent in 44 per cent, and higher than 20 per cent in 20 per cent of a series of patients¹⁷²⁵.

In general, the state of the eye grounds permits a prognostic evaluation of the individual case in that the severity of the clinical course is roughly paralleled by that of the retinal lesions, papilledema being of particularly ominous significance^{724, 1718}.

Role of the Adrenosympathogenic Neurohormones

The resemblance of the basic clinical features of malignant hypertension with those of essential hypertension is apparently paralleled by similar analogies regarding neurosecretory, adrenocortical and renal pathogenic factors. It has been emphasized before that the syndrome of essential hypertension is mimicked by both pheochromocytomas and adrenal cortical tumors and that all symptoms can be brought to disappearance by the timely removal of either of them. A joint operation of sympathomimetic catecholamines and mineralocorticoids in the development of essential hypertension was deduced from this and from other indications (p 308). The same can be said concerning malignant hypertension insofar as its clinical and morphological characteristics, including retinal and renal lesions of all degrees, have been observed both in cases of pheochromocytoma^{114, 140, 2477, 2517, 2521, 2509} and of Cushing's syndrome^{340, 535, 939, 1223, 2173} with partial or complete normalization after surgical extirpation of the respective tumors (p 87, 101).

A prominent participation of adrenosympathogenic neurosecretory catecholamines in the origin of malignant hypertension is suggested by the following observations:

(a) Despite the general stability of the high blood pressure of malignant hypertension, it is possible, at least in some cases, to lower it considerably, even to normal levels, by phenobarbital¹⁷²³, tetraethylammonium²¹¹⁴, adrenolytic drugs^{1460, 2492, 2493} and spinal anesthesia¹⁷⁴⁴.

(b) Extensive sympathectomy is capable of significantly improving the renal^{150, 1501, 2177} and ocular^{724, 2503} status and the length of survival time

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Both 11-oxo- and 11-desoxycorticoids were found in increased amounts in the urine of patients with malignant hypertension^{220a}. Furthermore, there exist some experimental and clinical observations which are indirectly suggestive of a significant participation of adrenal corticoids in the pathogenesis of this syndrome, even if only in a supporting capacity. Experiments consisting of the administration of DCA and of stressful situations in unilaterally nephrectomized, salt-fed rats produced arteriolar hyalinization and necrosis^{107, 207} resembling those of malignant hypertension. The dramatic cure of a case of typical malignant hypertension performed by Green and coworkers¹²² through bilateral adrenalectomy, and the immediate return of the symptoms when DCA was administered, serve as impressive indications of the indispensability of adrenal mineralocorticoids in maintaining, if not primarily causing, the syndrome of malignant hypertension. In case the hypothesis of an abnormal renal retention in the body of otherwise excreted corticoids¹²³ should prove tenable, this might account for an exaggeration of mineralocorticoid-supported pressor and cardio-angiotoxic mechanisms through actual accumulation of such hormones. The increase of myocardial intracellular sodium concentration, found in animals with experimental renal hypertension²²⁰, is likewise suggestive of augmented mineralocorticoid activity.

The behavior of sodium excretion and of the serum sodium level is of minimal informative value as far as the crucial question of intracellular sodium deposition under mineralocorticoid influence is concerned. Concomitant renal glomerular and tubular lesions can cause either a retention or a loss of sodium²²⁴, neither of which reflects clearly the intracellular electrolyte changes which exert probably a decisive influence upon the hemodynamic state of the cardiovascular system.

On the other hand, the withdrawal of sodium from the diet proved an efficient therapeutic measure in a considerable number of cases with malignant hypertension^{125, 222, 223} and was also found effective in normalizing the blood pressure of renal hypertensive animals^{104a}. It seems to achieve a similar effect as adrenalectomy, namely a specific alteration in the electrical membrane potential of the cardiovascular cells which, in turn, is believed to cause a decrease of their contractility (p. 25, Fig. 38, 39).

Role of Renal Factor

It must be emphasized that a severe elevation of blood pressure, even

such as glomerulonephritis, pyelonephritis, intercapillary glomerulo-sclero-

(p. 317), even though only in patients whose anatomical lesions and renal excretory failure have not progressed to an advanced stage^{1587, 3179}.

(c) Post-mortem studies^{1571, 3191} disclosed indications of a spastic constriction of otherwise intact renal arterioles in the earlier stages of the disease. Renal functional insufficiency and even full-fledged uremia were observed in some patients whose renal arterioles showed only relatively slight hyalinization and no necroses^{157, 723, 1859, 1735, 2401}. A neurogenic renal vasoconstriction was considered by some authors^{1571, 3191} in those cases in which anatomical vascular lesions in the kidneys are not prominent. Beside the possibility of abnormally intense sympathetic impulses reaching the kidney vessels, perhaps as a result of cerebral vascular ischemia^{1193, 1784, 2942}, a locally toxic action of circulating catecholamines in the renal arterioles may be thought of (p. 83 ff.) which would further intensify renal vasoconstriction^{134, 1429, 2344, 2791, 3194a} and contribute to the development of renal arteriolar lesions and impairment of glomerular function²³⁴⁴.

(d) An augmented excretion of urosympathin was observed in cases of "chronic nephritis"⁷³⁵⁹ and interpreted as being due to an over-production of hydroxytyramine and of sympathomimetic catecholamines. An imbalance in the ischemic kidney between the O_2 -dependent amine-oxidase and the O_2 -independent dopadecarboxylase action in favor of the latter was held responsible for the assumed excess formation of urosympathin¹⁸³³.

(e) In all advanced cases of renal excretory insufficiency, excessive amounts of catecholamines were found in the blood^{2476, 2692} (p. 478).

(f) The occurrence of diffuse degenerative, partly necrotizing arteriolar changes in cases of pheochromocytoma and after prolonged experimental administration of epinephrine^{273, 369, 1909, 2499} and of large doses of epinephrine-potentiating thyroxine³⁰⁴⁰ suggests that the vascular lesions of malignant hypertension may likewise be due to the injurious influence of catecholamines related to epinephrine whose locally hypoxiating and ultimately necrotizing effects are well known (p. 11 ff., 15 ff.).

(g) The hemodynamic situation (increased peripheral resistance, no increase of minute volume^{1420, 2942} except in the uremic stage¹³²⁰) differs from that elicited by epinephrine and corresponds rather to that caused by nor-epinephrine.

Role of the Adrenal Corticoids

In connection with the problem of essential hypertension and of hypertension in Cushing's syndrome, it was pointed out (pp. 103 and 285 ff.) that the intracellular deposition of sodium under the influence of adrenal mineralocorticoids seems to constitute an important factor in the maintenance of elevated blood pressure levels.

nine in the ischemic kidney^{267, 1559, 2149, 2465}. The significance of VEM²¹²⁵ and pherentasin²⁰⁴⁹ remains to be elucidated.

Ad (2) · The retention in the blood of various potentially toxic substances, such as urea, creatinine, phenols, guanidine, potassium and others, due to renal excretory insufficiency, has long been suspected^{264, 990} as possibly contributing to the uremic syndrome, but it seems doubtful that any of them be causally responsible for the development of those cardiovascular alterations which are characteristic of the clinical and pathologic anatomical picture of malignant hypertension.

In 1944, the writer²⁹³ described the *regular presence of excessive amounts of catecholamines in the blood of practically all patients with uremia*. This material displayed the same colorimetric and adsorbability properties as epinephrine and nor-epinephrine and proved highly toxic to the heart (p 478 ff) More recently the same author and his co-workers²⁹⁹ found the urinary excretion of total catechol compounds in uremic cases within or below the normal range. This seems consistent with the assumption of a renal retention of adrenosympathogenic catecholamines, which is also supported by the observation of "false positive" benzodioxane tests in uremic patients^{40, 117, 124, 269, 272}. The chemical and pharmacodynamic nature of the substances in question is being further investigated at the present time. The fact that pressor substances could be extracted with certain techniques from the blood of patients with malignant hypertension and chronic glomerulonephritis^{72, 227} but not from that of normal individuals^{72, 244} and only occasionally from that of patients with essential hypertension^{72, 244}, suggests a possible identity of these substances with the excess catecholamines detected by the writer in uremic blood and in the blood of some patients with renal hypertension without uremia.

It seems possible that an early exaggerated neurosecretory discharge of sympathogenic catecholamines into the walls of the renal arterioles may start a
tion of -production
renal ar lesion of
hypoxia plus mechanically damaging effect of elevated hydrostatic pressure—uremia—retention of adrenosympathogenic catecholamines—further chemical injury to renal and other arterioles and the heart—complete renal functional breakdown with or without cardiac failure—death.

The above-outlined concept of the pathogenesis of malignant hypertension attributes again a leading role to the toxic adrenosympathogenic hormones, similar
and assumed in ess
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renal ischemia and resulting nephrogenic pressor mechanisms which are

sis, congenital malformations, renal infarction, periarteritis nodosa and others^{724, 2014}. Nevertheless, the fact stands out that practically all cases of malignant hypertension are associated with some degree of renal functional deficiency. In the absence of demonstrable anatomical lesions, spastic constrictions of the renal arterioles have been suspected as causing local ischemia^{1461, 2122}. This latter condition is known since the classical experiments of Hartwich¹¹⁰⁴ and of Goldblatt¹¹⁷⁴, to produce the nephrogenic type of hypertension. The non-participation of the renal nervous supply in the presumable elaboration of pressor substances by kidneys whose blood flow has been mechanically impaired^{740, 851 873, 1049 1173} cannot be held against the possibility that neurogenic, vasoconstrictory renal ischemia may elicit specifically nephrogenic hypertension. The experimental production of hypertension by prolonged electrical¹³²⁷ and mechanical-chemical²⁴⁷ stimulation of the renal nerves illustrates this point.

The importance of some degree of renal excretory insufficiency for the development of diffuse necrotizing arteriolar changes can be concluded from Goldblatt's observation that in his hypertensive dogs significant arteriolar alterations "of the malignant phase" did not appear unless "a combination of impairment of renal function and increased bursting tension of the vascular wall" was produced¹¹⁷³. The provocation of severe necrotizing arteriolar changes in dogs during the administration of a high fat diet was likewise dependent on the simultaneous production of renal insufficiency¹³³³.

The exact mechanism of renal hypertension and of its complications is still an unsolved problem, despite the enormous amount of work which was devoted to its clarification. Two main factors have to be considered: (1) *production of a pressor substance or substances by the angiospastically or anatomically ischemic kidneys*; (2) *retention of pressor substances, originating outside of the kidney tissue, due to renal excretory insufficiency*.

Ad (1): It is beyond the scope of the present discussion to dwell on the subject of renin formation which has been extensively presented by Braun-Menéndez²⁷⁸ and whose importance for clinical hypertension has become rather questionable^{19 736 1067 1263 1377 2012 2304} except apparently regarding malignant hypertension in which the related "hypertensin" was found to be greatly increased in the blood^{1692a}.

Selye's technique of the "endocrine kidney" (unilateral mechanical reduction of renal vascular hydrostatic pressure to a level prohibitive of glomerular filtration and resulting in obliteration of the tubuli) produces hypertension and "generalized vascular hyalinization in the opposite kidney as well as in extra-renal tissues throughout the vascular system"²²⁷⁷. The character of the substance or substances producing these lesions is unknown. One possibility might be an excess formation of the moderately pressor hydroxytyramine (precursor of nor-epinephrine) from dihydroxyphenylala-

Treatment

While only few years ago malignant hypertension was regarded as an utterly hopeless condition, not even worthy of any vigorous therapeutic attempts, the situation has changed considerably since a growing insight into contributing neurosecretory and hormonal mechanisms encouraged systematic attacks on some of these individual factors in an effort to break the vicious circle of mutually aggravating detrimental influences.

Sympathectomy, although by no means as radically curative as removal of a pheochromocytoma, proved useful in ameliorating even severe retinal lesions^{191 2418}. Patients with advanced renal insufficiency are usually excluded from sympathetic surgery but improvement of a partially impaired renal functional status was observed in the following respects and percentages in a large series of patients, operated on by Smithwick²¹⁷⁷: albuminuria improved in 60 per cent, the urine sediment improved in 65 per cent, PSP-excretion improved in 70 per cent, ability to concentrate improved in 90 per cent. Many of the cases included in this series were to be classified as "benign" hypertension, but the possibility of a betterment of renal function through sympathectomy can be assumed to account also for the prolongation of life of the patients with a definitely malignant hypertension. A comparison of the duration of survival of two series of such cases (146 medically treated^{2733 2418} and 112 others on which supradiaphragmatic sympathectomy has been performed by Peet²¹³⁷) reveals that the chance for patients with malignant hypertension to live for more than five years was increased from less than 1 per cent to 19 per cent as a result of the surgical intervention¹³⁸⁷ on the sympathetic neurosecretory system.

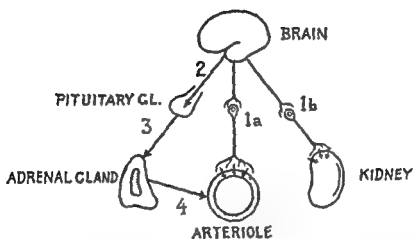
Despite such relative successes, the over-all results of sympathectomy in malignant hypertension have been justly described as "disappointing"⁷²¹. They only delay death from the renal, cardiac or cerebral complications but do not prevent it^{190 1357}. The limited improvements which can be achieved depend largely on an early and extensive¹²⁴¹ operation and careful selection of cases for which Smithwick²¹⁷⁹ has worked out an elaborate set of rules.

The failure of sympathectomy to alter the status and course of advanced cases significantly, suggests that the remaining sympathetic neurohormones and probably also other unknown substances of renal origin, in conjunction with sodium-retaining adrenal corticoids, continue to exert their injurious influences on the cardiovascular system.

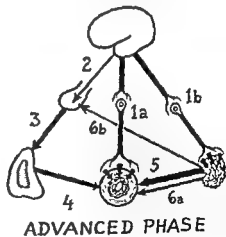
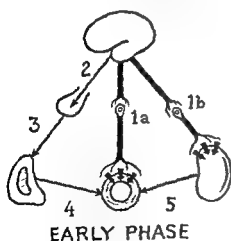
Kempner's rice-fruit diet^{1249, 1248 3319} and other sodium-poor diet forms¹⁷⁵⁴ were found to produce substantial improvements in various respects. Papilledema disappeared in 17 out of 23 cases, retinal hemorrhages in 39 out of

gradually consolidated by further anatomical lesions of the arterioles of the kidneys and complicated by an involvement of other organs, notably the brain and probably the adrenal cortex (Fig. 42).

NORMAL



MALIGNANT HYPERTENSION



(---) Sympathetic system
(---) system of

yielded even more effective normalizations of blood pressure, cardiac and renal status than adrenalectomy alone. It was found necessary to remove at least 90 per cent of the adrenal tissue in order to bring the blood pressure level of severe cases down to normal. (A spontaneous transition of renal hypertension to hypotension has been observed as a result of supervening Addison's disease with total destruction of the adrenal glands^{201a}.)

In conclusion, the application of various pyrogens may be mentioned as being capable of increasing blood flow²⁰², of diminishing peripheral resistance²⁰³, and of temporarily lowering the blood pressure^{204, 205}. According to Page and Taylor²⁰⁶, it is even possible to bring the signs of necrotizing arteriolitis to a standstill by treatment with bacterial pyrogens (Pyromen) in patients with malignant hypertension and with a renal functional depression not below 40 per cent of the normal average. With almost daily injections the treatment may have to be continued over months in order to bring the ocular changes, hematuria and proteinuria to more or less complete regression. Whether the life expectancy can be significantly improved by this treatment cannot be decided at this time. Its mechanism is not clearly understood.

Summary

The pathogenic neurohormonal and adrenocortical factors, presumably responsible for the rapidly progressing syndrome of "malignant hypertension" and for its causative necrotizing diffuse arteriolar lesions, seem to be qualitatively identical with those discussed in connection with the origin of "essential" hypertension. The main difference seems to rest in an earlier and quantitatively more intense renal involvement in malignant hypertension. The following sequence of events is tentatively assumed to produce the clinical syndrome: (a) initial neurogenic renal vasoconstriction, accompanied by a combination of general neurogenic plus nephrogenic (renal ischemic) hypertension, (b) neurohormonal hypoxie plus hydrostatic injury to the renal vessels, (c) excretory renal insufficiency, (d) retention of vaso- and cardiotoxic catecholamines and possibly corticoids; (e) further general vascular lesions, leading to renal (uremic), cardiac or cerebral vascular death.

Therapeutic measures intended to interrupt this sequence

... seems to be the most promising, if performed in a sufficiently early stage and if followed by life-long substitutive therapy with adrenal extracts, containing none or only a minimum of the mineralocorticoids which potentiate the pressor action of the adreno-sympathogenic catecholamines.

55, exudates in 42 out of 70¹⁷⁴³. Of 15 cases with a high NPN, seven showed an improvement of kidney function and of hypertension¹⁷⁵⁸. Headaches were uniformly relieved by salt restriction¹⁷⁵⁹. In view of the fact that some patients with renal failure tend to lose sodium because of a deficient tubular reabsorption, the use of a sodium-poor diet in patients with kidney damage must be carefully supervised by frequent serum sodium and urea determinations in order to avoid the consequences of a serious hyponatremia and concomitant azotemia^{1759, 2167, 2417, 2775, 3034, 3139} (p. 510). Cation exchange resins should not be administered in the presence of renal insufficiency. Because of the technical and psychological difficulties inherent in the prolonged application of practically sodium-free regimes and because of their inability to bring the progression of far advanced cases to a complete standstill, they too can only be considered as palliative measures, though sometimes surprisingly successful for a certain space of time.

The most heroic therapeutic approach, based on the recognition of the pathogenic role of adrenal mineralocorticoids, and foreshadowed by similar but less radical operations^{613, 703, 2430} consists of *bilateral adrenalectomy*, which was first performed by Green and co-workers¹²⁶² in 1948 in a case of malignant hypertension (maximally 270/140 mm) with albuminuria, hematuria, a PSP excretion of 44 per cent in two hours, multiple retinal hemorrhages and exudates, papilledema and cardiac enlargement. Fifteen months after the operation, on a daily substitution dosage of 0.5 mg DCA and 20 cc aqueous or 2 cc lipid adrenal extract, the blood pressures ranged from 120 to 150 mm systolic and 70 to 100 mm diastolic, the urine contained only traces of albumin, the PSP excretion in two hours was 59 per cent, retinal lesions had disappeared except for some scars, the heart size was normal and blood urea nitrogen was 12.5 mg per 100 cc.

Similar favorable results were reported more recently by other workers^{704, 3100a, 2864, 2710a} regardless of claims that this form of treatment lacks rational foundation³¹³³. In one series of 11 cases^{2710a}, 3 patients died after the operation; in the remaining 8, the systolic blood pressure fell 20-100 mm, the diastolic 10-50 mm. All were subjectively improved and the vascular resistance of the kidneys was found decreased. Four post-operative deaths occurred in another series of 12 cases^{3100a}, 3 showed a striking improvement of their blood pressure, in the 5 others the results were unimpressive, however.

In 8 out of 23 bilaterally adrenalectomized patients, the removal of about 90 per cent of the adrenal tissue was combined with thoracolumbar sympathectomy³⁶⁶⁴. This procedure which eliminated the sources of both types of noxious agents presumably involved in the pathogenesis of hypertension, namely mineralocorticoids and catecholamines, seems to have

This can be taken as another evidence of an excessive activity of the calorogenic adrenosympathogenic catecholamines in peripheral tissues, in accordance with experimental findings¹¹⁰ which indicate a central nervous regulation of general oxygen consumption.

Origin and Symptomatology

Concussion of the brain as the immediate cause of either sustained or paroxysmal hypertension was observed by the writer in two cases^{24,25}, one

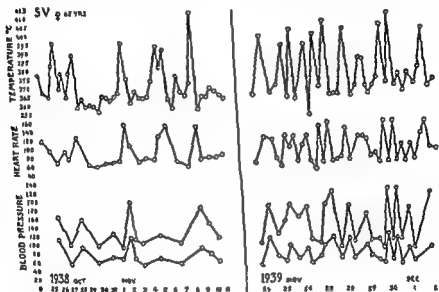


FIG. 43 Attacks of paroxysmal hypertension, tachycardia, and hyperpyrexia, elicited by two concussions of the brain (one year apart) in the same patient (After W. Raab, *Am Heart J* 37: 237, 1949)

of which presented a clinical picture closely resembling that of "diencephalic autonomic epilepsy" and of pheochromocytoma. It consisted of a long series (almost daily for four months) of violent attacks of systolic and diastolic hypertension, tachycardia, hyperpyrexia (Fig. 43), hypermetabolism (to plus 90 per cent), profuse perspiration, muscle pains, prostration and mental confusion. The latter was manifested, e.g., by incoherent and mis-spelled letters to the writer, one of which ended with the words "Heil Hitler!" (in 1939 when this might easily have been construed as a punishable joke by the censor).

The development of sustained hypertension after concussion is somewhat more frequently seen than the paroxysmal type^{201, 262, 277, 252}. The rise of the blood pressure to abnormal levels may be delayed for days or weeks

Primary Centrogenic Hypertension

General Principles

The central nervous system as a primary source of arterial hypertension has received only a minimum of attention in the Anglo-Saxon literature except for the consideration of psychogenic factors in the origin of essential hypertension. It is true that the number of cases of hypertension whose underlying pathogenic mechanism can be located unequivocally in the brain or cord is small by comparison with the multitudes of patients afflicted with other types of hypertension. Nevertheless, despite their numerical inconspicuousness, these unusual forms of clearly centrogenic hypertension deserve considerable interest in that they establish the fact that very marked elevations of the blood pressure can occur in the absence of primary renal, adrenocortical or peripheral vascular lesions on a purely cerebral or spinal nervous basis. Abnormal stimuli, arising in the central nervous system, are conveyed to the contractile cardiovascular target cells by means of two categories of hormonal mediators: (1) sympathomimetic catecholamines, discharged from the adrenal medulla into the circulation and from the post-ganglionic sympathetic fibers into their respective effector cells, (2) adrenocortical steroids, discharged into the circulation under the influence of adrenocorticotrophic secretion by the anterior pituitary which is governed by hypothalamic neurohormonal stimulation (encephalin? p 352)

The types of central nervous derangements which are capable of eliciting hypertensive crises or sustained hypertension are quite varied (Fig. 27, III, IV). Some of them are believed to have a state of cerebral ischemia in common which is known to cause blood pressure rises (p 267 ff.), especially also in conjunction with local mechanical irritation³³⁴⁸. Acutely increased intracranial pressure may likewise elevate the systemic blood pressure⁶³¹.²⁴²⁴ Indications of an enhanced epinephrine secretion by the adrenal medulla under the influence of cerebral injury and anoxia have been described by various authors⁷⁹⁰, ⁸⁵⁰, ¹⁰⁴⁷. However, the principles of cerebrospinal regulation of sympathetic activity can be assumed to apply also to the process of post-ganglionic neurosecretion of nor-epinephrine. Not infrequently the paroxysmal blood pressure "crises" of cerebral or spinal origin are accompanied by other clinical signs of a "sympathetic storm", such as pallor or flushing, perspiration, anxiety, tachycardia, fever, epigastric pain, etc. Thus, they display a remarkable, sometimes misleading²¹⁷ resemblance to cases of pheochromocytoma. Like the latter, some patients with primary centrogenic hypertension have an abnormally increased metabolic rate.

This can be taken as another evidence of an excessive activity of the calorogenic adrenosympathogenic catecholamines in peripheral tissues, in accordance with experimental findings¹²¹⁰ which indicate a central nervous regulation of general oxygen consumption.

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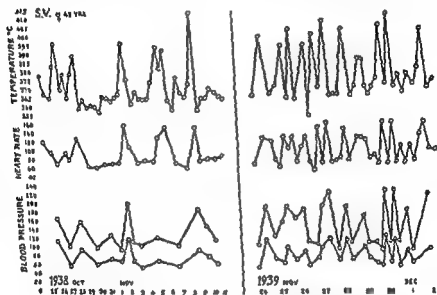


FIG 43. Attacks of paroxysmal hypertension, tachycardia, and hyperpyrexia, elicited by two concussions of the brain (one year apart) in the same patient (After W Raab, *Am. Heart J.* 37: 237, 1949)

of which presented a clinical picture closely resembling that of "diencephalic autonomic epilepsy" and of pheochromocytoma. It consisted of a long series (almost daily for four months) of violent attacks of systolic and diastolic hypertension, tachycardia, hyperpyrexia (Fig 43), hypermetabolism (to plus 90 per cent), profuse perspiration, muscle pains, prostration and mental confusion. The latter was manifested, e.g., by incoherent and misspelled letters to the writer, one of which ended with the words "Heil Hitler" (in 1939 when this might easily have been construed as a punishable joke by the censor).

The development of sustained hypertension after concussion is somewhat more frequently seen than the paroxysmal type¹²¹² and ¹²¹³ ¹²¹⁴ ¹²¹⁵. The rise of the blood pressure to abnormal levels may be delayed for days or weeks

after the provoking accident and the duration of a more or less labile hypertensive state may extend over weeks or years. A large survey of post-concussion cases⁴⁶³ revealed that 83 per cent of a group of 81 such persons (average age 29 years) had a pressure level higher than their respective age standard, with a maximum of 190 mm Hg systolic and an average of 146.5/91.7 mm, measured an average 4.5 years after the accidents. Seventy-eight per cent of those individuals who were submitted to the CO₂-inhalation test, introduced by the writer²⁵⁵, showed a reaction greater than the normal average of their age groups. Tests for increased vasomotor irritability, such as hyperventilation, carotid sinus pressure, breath-holding, smelling ammonia and the cold pressor test, were found exaggerated by the writer in one case during the hypertensive phase after concussion, while all reactions reverted to normal when the blood pressure fell to its original level (Fig. 44). It is worthy of note that intense rises of blood pressure could be produced also in animals by means of experimental concussion of the brain^{721, 2618}.

The activation of a pheochromocytoma to hypertensive paroxysms four months after a concussion in one patient was suspected as being causally linked with this accident²⁵⁶⁹.

Effects of *direct cerebral injury* upon the cardiovascular system were studied by several European investigators during and after the two World Wars. Temporary elevations of the blood pressure^{276, 2064} with increased reflexory pressor responses and hypertensive crises²⁰²³, occasionally connected with pulmonary edema²²⁹⁰, were found to be a rather frequent occurrence in the early stages following cerebral injury. Examination of 250 cases (age 20–35 years) two to five years after the brain had been injured, revealed only moderate and occasional elevations of the systolic and diastolic blood pressure in 15 per cent of the patients¹⁰⁴⁵. The hemodynamic status (peripheral resistance, cardiac output) was not significantly altered but abnormal responses to the circulation tests of Schellong²³⁷⁴ and the writer²⁶³⁴ were frequently observed¹⁰³⁵. Augmentations of the basal metabolic rate, while present in the great majority of cases who had received cerebral injuries two to nine months previously²²³, could be detected in only 28 per cent a few years later¹⁰³².

Therapeutic *frontal lobotomy* was seen to be followed by exaggerated pressor and pulse pressure responses to infused epinephrine, yet the blood pressure level of hypertensive patients seems to be favorably influenced by this operation²⁸⁰⁶.

Encephalography is frequently accompanied by elevations of the blood pressure which may be quite marked²²², and which are sometimes followed by rather irregular alterations of the cardiovascular responses to various stimuli¹⁰³⁴.

Sudden high rises of the blood pressure may take place sometimes as an aftermath of *spontaneous cerebral hemorrhages*^{221, 222, 227, 269, 281}, also if the hemorrhage is located in the medulla oblongata²¹⁹. They were interpreted as being due to both mechanical irritation and to ischemia of central vasoconstrictor areas¹⁶⁹.

A.K. ♀ 31 YRS.

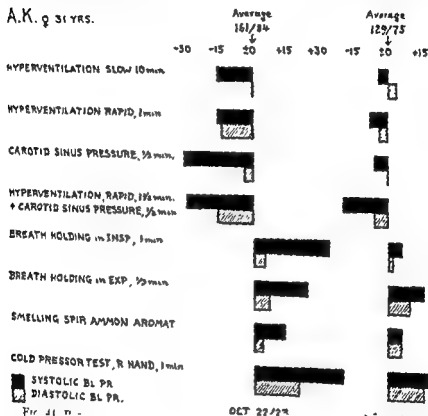


Fig. 11 n -

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As far as cerebral ischemia is concerned, its common occurrence in arteriosclerotic individuals and its significance for the pathogenesis of neurogenic essential hypertension have been discussed on p 267 ff, 272.

Intracranial tumors which are not directly related to the vasoconstrictor areas of the brain, usually do not tend to elevate the blood pressure level²⁰. The central vasomotor regulatory apparatus seems to become adjusted to the gradually developing abnormal situation, except in occasional cases

after the provoking accident and the duration of a more or less labile hypertensive state may extend over weeks or years. A large survey of post-concussion cases³⁶³ revealed that 83 per cent of a group of 81 such persons (average age 29 years) had a pressure level higher than their respective age standard, with a maximum of 190 mm Hg systolic and an average of 146.5/91.7 mm, measured an average 4.5 years after the accidents. Seventy-eight per cent of those individuals who were submitted to the CO_2 -inhalation test, introduced by the writer²⁵⁵, showed a reaction greater than the normal average of their age groups. Tests for increased vasomotor irritability, such as hyperventilation, carotid sinus pressure, breath-holding, smelling ammonia and the cold pressor test, were found exaggerated by the writer in one case during the hypertensive phase after concussion, while all reactions reverted to normal when the blood pressure fell to its original level (Fig. 44). It is worthy of note that intense rises of blood pressure could be produced also in animals by means of experimental concussion of the brain^{721, 2618}.

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war time²²¹. Increased cold pressor reactions were recorded in the majority of ship-wrecked seamen whose ships had been torpedoed several months to two years earlier¹¹⁰⁴.

A participation of both epinephrine discharges and adrenal cortical steroid secretion (probably epinephrine-induced) under emotional stress was suggested by the pattern of cardiovascular reactions and the accompanying eosinopenia of medical students immediately before examinations, as reported by Humphreys and the writer¹⁰⁰². Other details regarding psychogenic hypertension have been mentioned on p. 273.

Less common, but not less violent than the blood pressure paroxysms of cerebral origin, are those which are caused by *functional disorders or injuries of the spinal cord*, apparently through involvement of the spinal sympathetic centers, e.g., in cases of *tabes dorsalis*. Such episodes, occurring in conjunction with the "gastric crises" of tabetic patients, were described by Pal in 1903 under the term "vascular crises"¹²⁰³. The syndrome was later confirmed by others with or without gastric participation^{144, 217, 329, 1218, 1119, 1646, 2145, 2101}. The systolic and diastolic pressures of such patients move parallel, either in short transient spikes (e.g., from 120/80 to 300/190²¹⁷), or they persist on high levels for days at a time^{119, 2107}, occasionally alternating with postural hypotension¹⁵⁰². The similarity of these episodes with the hypertensive paroxysms of pheochromocytoma has prompted erroneous surgical intervention²¹⁴. Lesions of the spinal cord, especially if located above the level of the fifth dorsal segment, are attended by a marked instability of the blood pressure, not infrequently amounting to full-fledged extreme hypertensive crises (e.g., from 90/70 to 220/140¹²⁷⁴), which are usually accom-

panied by micturition of the bladder or rectum^{1424, 2007, 2174}.

Treatment

The indications for therapeutic attempts in cases of centrogenic hypertension are largely determined by (a) the nature and therapeutic amenability of the underlying pathological process in the central nervous system, (b) the severity and type of the hypertensive manifestations themselves.

Conditions accompanied by augmented intracranial pressure may be accessible to surgical correction and drainage, emotional situations may yield to psychotherapy, *tabes dorsalis*, to specific antiluetic treatment. Moderate and transitory elevations of the blood pressure after cerebral injury to the brain stem may be treated by aggressive measures. Violent hypertension with high blood pressure levels on the other hand constitute a serious problem for which no systematic therapeutic procedure has yet been worked out. However, experiences

in which the systemic blood pressure rises in proportion to the increased intracranial pressure¹⁸⁹¹.

Dramatic attacks of paroxysmal hypertension of the type of "diencephalic autonomic epilepsy", described by Penfield²⁵⁶⁰ in a case of a thalamic tumor, have also been observed as the result of a small cyst in the thalamus⁵⁶⁵. In this fatally ending case, the blood pressure oscillated between 88/40 and 220/160 mm Hg and the paroxysms were accompanied by tachycardia, hyperpyrexia and other neurovegetative manifestations.

A comparatively common event is the appearance of hypertension in connection with *encephalitis* and *poliomyelitis*^{1032, 1719, 2076, 2569}, especially in cases of ascending poliomyelitis when the process has reached the medulla oblongata^{2447, 2921}. If the patient survives, the cardiovascular status may revert to normalcy within several months²⁹²¹. Basal metabolic rates as high as plus 126 per cent, plus 130 per cent and plus 180 per cent were recorded in one post-encephalitic case. Thyroidectomy failed to improve any of the clinical symptoms¹⁰³². Steep ascents of the blood pressure were observed as a sequel of *meningococcal meningitis*²⁵²⁰ and an increased reactivity of the vasoconstrictor centers, as estimated by the cold pressor test, was seen in patients with *chronic syphilitic meningo-encephalitis*¹⁹⁵.

Carbon monoxide poisoning may be followed by hypertension^{2475, 3331} of apparently centrogenic origin.

The development of sustained arterial hypertension as a result of repeated *sensory and emotional shocks* was demonstrated in rats exposed to acoustic stimulations (air blasts)^{904, 2280, 2692}. A comparable phenomenon in humans, designated as "blast hypertension" by Ruskin²³⁹⁷, was observed by that author in the majority of the victims of the Texas City explosion disaster in 1947, even in those who were physically unharmed. Hypertension was recorded in some as early as one hour following the catastrophe. In 57 per cent of 180 cases, the diastolic pressure was 95 mm or higher. The cold pressor reaction was exaggerated in many of the subjects examined. Four to seven months later, 22 per cent of 111 follow-up cases were still hypertensive²³⁹⁶. Among British front-line soldiers in the North African campaign, a "battle pressure" of more than 160 mm systolic was observed in 38 per cent and a diastolic pressure of more than 100 mm in 27 per cent. Two months later, 85 per cent of those having displayed hypertensive levels were back to normal¹²²². Hypertensive readings were also recorded in 23 to 28 per cent of Finnish soldiers in the front line. Only 14 per cent of those in less exposed positions displayed hypertensive levels⁸⁴². Similar data were obtained among troops of the German army^{2916, 3310} and the Soviet army¹¹²⁴ during World War II and among the armed forces involved in the first World War (lit., see ⁴⁸⁷). Among United States Navy personnel who had shown a slightly elevated pressure years before, 74 per cent presented systolic hypertension and 25 per cent a diastolic pressure of 100 mm during

war time²²⁴. Increased cold pressor reactions were recorded in the majority of ship-wrecked seamen whose ships had been torpedoed several months to

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Conditions accompanied by augmented intracranial pressure may be accessible to surgical correction and drainage; emotional situations may yield to psychotherapy, tabes dorsalis, to specific antiluetic treatment. Moderate and transitory elevations of the blood pressure after concussion or injury to the brain, encephalitis and emotional shock do not require any aggressive measures and are likely to subside within a foreseeable period of time. Violent hypertensive crises and occasional persistent high pressure levels on the other hand constitute a serious problem for which no systematic therapeutic procedure has yet been worked out. However, experiences

gathered from individual cases^{217, 565, 1052, 2686}, showed that sedatives (sodium amytal, pentobarbital, evipal), administered parenterally, are capable in some instances of cutting short the paroxysms, even if only for a limited time space. Dihydrogenated ergot alkaloids (CCK-179 and others) appear theoretically suitable because of their simultaneous central inhibitory and peripherally adrenergic blocking properties. For prevention of attacks as well as for depression of an already elevated centrogenic blood pressure, dibenamine, or better still, one of its less toxic newer congeners, may become the remedy of choice because of potent adrenosympatholytic action and prolonged effectiveness; but no data on the use of these drugs in clear-cut centrogenic cases are yet at hand. Tetraethylammonium (400-1000 mg intramuscularly) was found useful in some instances of hypertensive paroxysms after spinal cord injury²²⁷⁵. Extensive sympathectomy has been recommended but not yet tried in such cases.

Summary

The existence of primary centrogenic mechanisms of arterial hypertension is illustrated by the occurrence of paroxysmic or sustained, sometimes extreme, elevations of the blood pressure in connection with cerebral concussion or direct injury to the brain, cerebral hemorrhage, tumors of the thalamus, encephalitis, poliomyelitis, CO poisoning, sensory or emotional shocks, tabes dorsalis and other lesions of the spinal cord.

The hemodynamics and general symptomatology of the hypertensive crises after concussion and in cases of thalamus tumors and spinal cord lesions, are practically identical with those of hypertensive paroxysms caused by pheochromocytomas. This fact, as well as the marked non-thyrogenic elevations of the basal metabolism which some of the centrogenic hypertensive syndromes have in common with pheochromocytomas, and the occasional hypothalamic manifestations of the latter, give proof of close mutual functional relations between the central nervous system and the adrenosympathetic neurosecretory system.

A secondary supporting participation of the adrenal cortex in the maintenance of the sustained types of centrogenic hypertension is suggested by certain experimental and clinical observations.

In the symptomatic treatment of primary centrogenic hypertension, particularly in the troublesome paroxysmic forms, barbiturates and tetraethylammonium chloride have proved useful, some of the new, less toxic dibenamine congeners may be expected to offer more prolonged relief.

The centrogenic and neurosecretory mechanisms of arterial hypertension are in need of a much more thorough investigation than has been accorded to them so far.

"Essential" Hypotension

Definition and General Principles

No agreement has been reached to this day concerning the futile question as to where the artificial borderline between "normal" and "hypotensive" should be drawn, if at all, nor whether "essential" hypotension is a disease in the strict sense of the word or merely a constitutional peculiarity. The suggested lower limits for the "normal" range of systolic pressure vary between 90 and 120 mm, of the diastolic pressure between 50 and 80 mm, and accordingly the statistical incidence of "essential" hypotension was placed somewhere between 2 and 55 per cent²⁷¹.

A particularly large survey (10,833 persons) in which the dividing line was arbitrarily set at 110/70 mm²⁷², revealed the existence of pressure levels lower than this in 25 per cent (systolic) and 34 per cent (diastolic) of all the age groups taken together. The incidence among young women was higher than in any other groups, but otherwise the distribution of hypotension was a rather even one throughout all age categories. Low weight and slender build are characteristic for hypotensive individuals²⁷³⁻²⁷⁵. A hereditary and family background was stated in some instances²⁷⁶⁻²⁷⁹. The blood pressure variations, observed in the same persons from year to year over longer periods, were conspicuously small²⁷³, pressure reactions to emotional situations seemed insignificant and gradual elevations toward hypertensive levels occurred only in exceptional cases^{280, 281}.

Many hypotensive individuals complain of fatigue, headache, dizziness and other vague symptoms which were considered as a specific syndrome by Laan and Blondel²⁸² and others, but it was pointed out that practically the same symptoms are frequently present in essential hypertension²⁸³. They are probably not caused by the hypotensive hemodynamic state per se²⁸⁴, although there seems to be a certain proportionality between the degree of hypotension and the occurrence of subjective discomfort²⁸⁵. A low blood pressure level does not necessarily interfere with physical fitness, as illustrated by the existence of marked hypotension in some athletic individuals and sportsmen^{282, 286}, and by the prevalence of low blood pressure among certain primitive and less over-civilized races, such as the Australian aborigines²⁸⁶, East African natives²⁷⁸, Puerto Ricans²⁸⁷, Arabs²⁸⁸ and Zuni Indians of New Mexico²⁸⁹. Some of these lead very strenuous lives and display remarkable physical endurance until their old age. In view of such inconsistencies, the fatigability and weakness of many hypo-

tensive individuals was interpreted as being due, at least in part, to sedentary living habits and lack of physical exercise²⁸²⁴.

The relative mortality rate of hypotensive persons is statistically lower than that of normotensives^{295, 1603} and Robinson goes so far as to declare that "hypotension is not a disease; it is an ideal blood pressure level"²³³³.

Neurohormonal and Hormonal Aspects

The causal relations between certain well-defined endocrine abnormalities, especially hypoadrenocorticism and hypopituitarism on one hand, and arterial hypotension on the other, have been discussed on pp. 112 and 178. Up to the present, the question as to whether or not similar neuroendocrine and hormonal mechanisms are involved in the origin of essential hypotension does not seem to have been approached systematically by means of direct hormone assays, electrolyte studies and the like. However, certain hemodynamic and metabolic details of the clinical picture permit some indirect tentative conclusions, particularly concerning the state of neurohormonal activity.

The frequent presence of bradycardia^{2234, 2769}, of a low stroke volume and cardiac output²⁷⁶⁹, of a low basal metabolism^{259, 2234} and of a low blood sugar level are consistent with the assumption of a generally low sympathetic tone and prevalence of vagal influences²⁷⁶⁹.

In view of the results of animal experimentations which showed that the vessels of the skeletal musculature can dilate under hypothalamic control³⁵² and that the blood pressure can be lowered by stimulation of certain areas of the hypothalamus^{1499, 3242}, a central nervous derangement was postulated for the explanation of essential hypotension.

While no facts are at hand which might tend to invalidate this concept, one must not lose sight of the possibility that an abnormal diminution of cardiovascular contractile power can occur in the face of a normally functioning neurosecretory system if the contractile cells are altered in a way which would impair their dynamic response to normal or even intensified adrenergic stimuli. Apart from theoretically conceivable but not proven primary abnormalities of the physicochemical structure of cellular protoplasm and membrane permeability, the most important factor capable of diminishing cardiovascular contractility is a deficiency or imbalance of adrenal corticoids at the expense of the mineralocorticoids and of intracellular sodium retention. Here again no directly conclusive data are available which would establish the participation of such a hypoadrenocortical element, but the frequently observed smallness of the heart²⁷⁶⁹, the above-mentioned low oxygen consumption and blood sugar concentration are at least compatible with its possible existence in hypotension. Furthermore, the administration of DCA^{2945, 3214} proved more rapidly and more strikingly

effective in raising the blood pressure in a few cases treated, than one might expect in individuals with normally functioning adrenal glands. Even salt intake alone is said to elevate the blood pressure in such cases¹¹⁴.

These scant and fragmentary data are only straws in the wind. Yet they seem to hint at the probability that essential hypotension, while not a "disease", might constitute the cardiovascular dynamic expression of a pattern of low level function of the cooperating neurohormonal and adrenal cortical mechanisms (p 25 ff) which are jointly responsible for the maintenance of the cardiovascular tone. It has been pointed out that both asthenic hypotensive individuals and highly trained athletes have features of "vagotonicity" in common¹¹⁵. The resemblance is only a superficial one, however, in that the adrenergic-cholinergic equilibrium seems to be established at different levels in these two types. The athlete, although possessing a strong vagal tone, maintains simultaneously also a potent sympathetic (neurosecretory) functional reserve to draw upon if needed, an advantage which the untrained asthenic hypotensive person seems to lack.

In principle, the factors causing the "essential" form of hypotension appear to be qualitatively related to those put into effect more acutely by certain pathological conditions, such as infectious diseases, anemia, protein deficiency, cachexia, etc., all of which are frequently associated with a lowering of the blood pressure, supposedly on the basis of an exhaustion of the adrenal cortex.

As far as alimentary protein deficiency is concerned, it was statistically shown to depress markedly the blood pressure level during the post-war years of malnutrition in Germany¹¹⁶, whereas the resulting high percentage of hypotensive cases gave way again to a more normal rate of incidence with increasing improvement of the food situation. The part played by proteins as building stones for the elaboration of the adrenocorticotrophic hormone of the pituitary^{117, 118}, and by amino acids as precursors of the sympathomimetic catecholamines¹¹⁹ may contribute to the blood pressure lowering effect of protein deficiency.

Summary

"Essential" hypotension is not a disease in the usual sense but a long standing, innocuous condition, without any objective signs or symptoms, and without any complaints and symptoms. The blood pressure level per se is not lowered. There is no evidence of any organic disease.

It is more conspicuous. No treatment is necessary for otherwise asymptomatic essential hypotension.

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The frequent presence of bradycardia^{2234, 2789}, of a low stroke volume and cardiac output²⁷⁸⁹, of a low basal metabolism^{259, 2234} and of a low blood sugar level are consistent with the assumption of a generally low sympathetic tone and prevalence of vagal influences²⁷⁸⁹.

In view of the results of animal experimentations which showed that the vessels of the skeletal musculature can dilate under hypothalamic control⁸⁵² and that the blood pressure can be lowered by stimulation of certain areas of the hypothalamus^{1499, 3241}, a central nervous derangement was postulated for the explanation of essential hypotension.

While no facts are at hand which might tend to invalidate this concept, one must not lose sight of the possibility that an abnormal diminution of cardiovascular contractile power can occur in the face of a normally functioning neurosecretory system if the contractile cells are altered in a way which would impair their dynamic response to normal or even intensified adrenergic stimuli. Apart from theoretically conceivable but not proven primary abnormalities of the physicochemical structure of cellular protoplasm and membrane permeability, the most important factor capable of diminishing cardiovascular contractility is a deficiency or imbalance of adrenal corticoids at the expense of the mineralocorticoids and of intracellular sodium retention. Here again no directly conclusive data are available which would establish the participation of such a hypoadrenocortical element; but the frequently observed smallness of the heart²⁷⁸⁹, the above-mentioned low oxygen consumption and blood sugar concentration are at least compatible with its possible existence in hypotension. Furthermore, the administration of DCA^{2945, 3214} proved more rapidly and more strikingly

both the systolic and diastolic pressures fall if the erect position is assumed in ¹⁸⁷ 188, ¹⁹³, the heart volume decreases (x-ray)^{191, 192} and the heart rate is not accelerated or may even be slow^{187, 190, 193}, except e.g. in the case of lumbar dorsal sympathectomy which does not include the cardiac nerve supply.

Beside the two above-described patterns of either prevailingly venous or prevailingly arterial tonus deficiency, there exist cases in which both conditions overlap. Regardless of the etiology and type of the underlying hemodynamic derangement, the subjective symptoms are essentially the same, consisting of giddiness, vertigo, faintness, and in extreme cases syncope, especially in the morning, after meals, and during exposure to heat.

Neurohormonal and Hormonal Aspects

The basic involvement of a sympathicotonic, i.e., neurosecretory deficiency, is obvious in those cases of postural hypotension which are artificially elicited by sympathectomy or ganglionic blockade. In the case of "arterial orthostatic anemia" with blood pooling on the venous side of the circulation, a participation of disturbances in the sympathetic nervous system is only conjectural. In "a sympathicotonic orthostatism", occurring in patients with diseases of the central nervous system, on the other hand, it may be assumed that interruptions of the reflex arc which is responsible for the liberation of pressor catecholamines from the efferent cardiovascular nerves, account for the failure to adjust the circulation to postural changes.

Little or no effect in such cases. The hemodynamic response to injected epinephrine was not found significantly altered^{187, 193}. In some of these patients, the simultaneous lack of perspiration points to a disturbance in the sympathetic system, deriving from hypothalamic lesions^{192, 194, 195}, in others, the spinal cord appears to be the primary seat of the trouble. Not too infrequently postural hypotension is observed in diabetic individuals who display also other criteria of autonomic nervous imbalance¹⁹⁶. No evidence seems to exist in favor of a fundamental derangement in the pressure-receptive areas of the carotid sinus¹⁹⁷. T-wave changes of the hypoxic type occur frequently in patients with postural hypotension.

Epinephrine stimulation (sympathogenic catecholamines) upon the heart muscle^{187, 198}.

The transitory forms of postural hypotension in convalescents after infectious diseases and other types of severe stress, are probably caused by a state of exhaustion of the pituitary-adrenocortical system and thus seem to

Postural Hypotension

Definition and General Principles

The phenomenon of postural or orthostatic hypotension, as described by Bradbury and Eggleston³⁶² and by Laubry and Doumer¹⁹³³, occurs both in individuals with "essential hypotension" and in normotensives^{1353, 2763}. It is caused by a failure of those regulatory mechanisms which adapt the circulation to the erect position in a way which maintains an adequate blood supply to the brain. Under the influence of the pressoreceptor apparatus of the carotid sinus, mediated by hypothalamic centers and by their sympathetic outflow, a change from the recumbent to the upright position or motionless standing is normally accompanied by constriction of both the venous system of the lower parts of the body and of the arteries³⁴. There is usually an increase of heart rate and cardiac output. In healthy individuals, the blood pressure may be somewhat lowered after standing up, but this fall should normally not be greater than 20 mm systolic and 5 mm diastolic, while the increase of the heart rate should not exceed 27 beats per minute²⁶.

Interferences with these regulatory reactions can take place in more than one way. Schellong²⁹⁷⁴ and Nylin²⁴⁸⁹ distinguish two types of "orthostatism". One type consists of an excessive pooling of blood in the veins below the heart due to lack of venous constriction^{2525, 3649, 4693} and/or to insufficiency of the venous valves, while the reflexory arterial constriction mechanism remains more or less intact. This condition, which was designated as "sympathicotonic orthostatism"²⁴⁸⁹ or "arterial orthostatic anemia"²³⁸¹ (referring to the sympathogenic arterial constriction), is generally characterized by an unchanged or elevated diastolic pressure and heart rate but decreased systolic pressure, pulse pressure and cardiac output, the latter features being caused by an insufficient venous return to the heart. This syndrome is relatively common among young, tall persons²³¹, individuals having varicose veins⁵⁰⁵ or anemia, convalescents and pregnant women²⁶⁴.

The other type of postural hypotension, designated as "asympathicotonic orthostatism"²²⁴⁹, is caused by a deficiency of compensatory arterial constriction^{2489, 3241}. It occurs as a primary syndrome, either entirely without any known pathogenic basis³⁶² or as a partial symptom of hypoadrenocorticism^{809, 1135, 3371} and of hypopituitarism^{586, 3215}, in cases of tabes dorsalis^{637, 3215, 3298}, syringomyelia, encephalomalacia, encephalitis¹⁸³¹ and Parkinson's disease, (ht., see ²⁴⁸⁹), and as an artefact after extensive sympathectomy^{1354, 2177, 2872, 3177, 3625} or after the administration of sympatholytic^{1701, 2434} and ganglionic blocking^{2114, 3156} agents. In this "asympathicotonic" condition,

Deficient venous constriction (blood pooling) and, particularly, deficient arterial constriction ("asympathicotonic orthostatism") can be caused by (a) an interruption of the reflex arc which regulates the neurosecretory discharge of sympathogenic pressor catecholamines into the cardiovascular muscle cells (this is the case in certain diseases of the central nervous system), (b) a diminished contractile responsiveness of the cardiovascular muscle cells to pressor stimuli due to adrenal cortical deficiency and to the resulting disturbance of the intra-extracellular electrolyte equilibrium (this is the case in hypopituitarism, Addison's disease and other states of hypoadrenocorticism, possibly also in some otherwise asymptomatic forms of postural hypotension)

Treatment may be undertaken by mechanical means, sympathetic stimulants and adrenocortical replacement therapy with addition of sodium chloride to the diet

be closely related to those seen in Addison's disease and hypopituitarism. In these instances there is no reason to suspect a significant disturbance in the sympathetic cerebrospinal reflex arc or in the neurosecretory activity of the post-ganglionic sympathetic fibers; rather does it seem likely that the underlying cause of postural hypotensive reactions consists in such cases of a diminished cellular contractile responsiveness to adrenergic pressor stimuli as a result of temporary adrenocortical functional deficiency (p 285 ff.). The weakened pressor effect of injected epinephrine in endocrine cases of this kind^{47, 623, 7384, 3770, 3371}, as contrasted with the normal epinephrine effect in neurogenic cases, and the therapeutic results obtained with DCA and salt administration (see below) point in the same direction.

Certain poorly defined relations to the functional state of the gonads are suggested by the occurrence of orthostatic hypotension during pregnancy²⁴⁵⁹ and at the age of puberty²⁹¹, as well as by a common lack of libido and of sexual potency^{825, 2459} in such individuals.

Whether and to what extent pituitary and adrenocortical factors take part in the origin of the otherwise asymptomatic forms of postural hypotension has not yet been investigated.

Treatment

Despite the basic harmlessness of the hemodynamic phenomenon of

nervous or endocrine disorders should be treated, if identifiable and amenable to therapy. The cardiovascular derangement can be favorably influenced by the following measures: (a) leg bandages or rubber stockings and an abdominal belt which should be put on before arising, (b) ephedrine hydrochloride or sulphate (25 mg), benzedrine (5 to 10 mg) and paredrine hydrobromide (60 mg) (lit., see ²⁴⁵⁹), to be used in the morning before getting up and during the day, (c) nor-epinephrine¹¹⁷³, (d) elevation of the upper end of the bed in order to "train" the cardiovascular system for a semi-upright position (20°)^{1654, 2177}; (e) administration of DCA and sodium chloride^{2099, 2331, 2624, 2945}, especially in cases presenting signs of adrenocortical underfunction. In one instance, nor-epinephrine infusions were found incapable of maintaining the blood pressure in erect position, while DCA elevated it to hypertensive levels in recumbency⁴¹⁶³.

Summary

Orthostatic hypotension and eventually syncope occur in a variety of conditions which interfere with the normal reflectory sympathogenic adaptation of cardiovascular dynamics to the erect position and thus with the maintenance of an adequate blood supply to the brain

lation. Therefore, the digital pressure test should always be applied with great caution.

The cardiovascular manifestations of the carotid sinus syndrome can be abolished by intramuscular injection of 1 mg of epinephrine. Atropine was seen to prevent the slowing of the heart but did not significantly affect the blood pressure reactions^{35,42}.

Whether or not an interference with sympathetic neuro-secretion is involved in the mechanism of the carotid sinus syndrome beside absolute vagus stimulation and increased cholinergic activity, cannot be decided at this time. No evidence is at hand regarding any other hormonal factors as taking part in the syndrome, except that insulin seems to increase the activity of the carotid sinus reflex and may even precipitate the occurrence of syncope^{25,36}.

Favorable, although not always completely curative, results have been achieved by denervation of the carotid sinus^{410, 414, 415, 417}, periarterial stripping⁴¹⁶, infiltration of the sinus area with novocaine³⁷⁰ and irradiation of a compressing tumor³⁶⁷. Nor-epinephrine has not yet been tried in patients with the carotid sinus syndrome but although it is in general much less toxic than epinephrine and might counteract the vasodepressant effects of the carotid sinus reflex, it does not seem advisable because of the associated secondary vagal action on the heart (see also the effect of atrioventricular conduction¹⁹⁴). Nor-epinephrine, on the other hand, stimulates the heart⁴¹⁸. It is capable of preventing carotid sinus-induced cardiac standstill and of accelerating ventricular action in the presence of complete block^{243, 412}. A combination of both substances might possibly be useful in a mode of application which would guarantee slow resorption and prolonged effectiveness.

Summary

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... manual pressure upon the pressoreceptor apparatus of the carotid sinus. Epinephrine prevents this reaction. A participating centrifugal derangement of sympathetic neurosecretory activity seems possible but has not been proven.

Carotid Sinus Syndrome

A syndrome, consisting of dizziness, blurring of vision, pallor, faintness, sometimes leading to unconsciousness and convulsions of one-half to three minutes' duration, occurs in certain individuals upon turning or lifting the head, shaving, swallowing, wearing a tight collar, and in other conditions, connected with some degree of pressure on the neck. It was identified by Weiss and co-workers^{970, 3542, 3544} as the result of an abnormal sensitivity of the carotid sinus reflex mechanism. Attacks, identical with those occurring spontaneously, can be elicited in such patients by relatively gentle unilateral digital compression of the carotid sinus (4-40 seconds)^{970, 2420, 2465, 3542}. They are usually accompanied by vagal cardiac manifestations, such as retardation, atrio-ventricular block and cardiac standstill and there may or may not be a precipitous fall of the blood pressure. In some instances cardiovascular signs are minimal or absent, yet the subjective symptoms may be essentially the same, a fact which was ascribed to a presumable transient local vasoconstrictory ischemia of certain cerebral areas³⁵⁴².

The systemic and the cerebral blood flow are reduced during the attacks but not to a greater extent than is often the case in patients with heart disease in whom no fainting and convulsions occur. Hence, the conclusion was reached that the suddenness of the hemodynamic changes rather than their magnitude seems to be responsible for the clinical features of the syndrome³⁵⁴².

In some cases, a mechanical basis for an abnormal sensitivity of the reflex mechanism could be detected, such as aneurysmal dilatation of one or both sinuses, a compressing tumor or lymph glands^{2163, 3542} or an adjacent foreign body¹¹⁴¹, but in others no anatomical abnormality seemed to exist. In some instances the seat of the functional disturbance, causing over-excitability or over-effectiveness of the reflex mechanism, may be located beyond the carotid sinus in the central synapses, the efferent neurons or even in the cardiovascular effector tissues, especially the heart itself²⁹⁹⁷. This is suggested by the fact that the syndrome, although altogether rare, occurs mostly in middle-aged or elderly persons with coronary sclerosis, with hypertension, and with damaged hearts^{3136, 3137} which are abnormally susceptible to vagal effects, leading to impairment of atrioventricular conduction and block³⁵⁶². In several cases, carotid sinus stimulation was seen to be followed by hemiplegia⁸² and in one by bilateral thrombosis of the anterior cerebral arteries²²²⁶, apparently as a result of the slowing of cerebral circu-

lation. Therefore, the digital pressure test should always be applied with great caution.

The cardiovascular manifestations of the carotid sinus syndrome can be abolished by intramuscular injection of 1 mg of epinephrine. Atropine was seen to prevent the slowing of the heart but did not significantly affect the blood pressure reactions^{25,27}.

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Favorable, although not always completely curative, results have been achieved by denervation of the carotid sinus^{61a, 210, 211, 212}, periarterial stripping¹⁹, infiltration of the sinus area with novocaine⁷⁰ and irradiation of a compressing tumor²⁶². Nor-epinephrine has not yet been tried in patients with the carotid sinus syndrome but although it is in general much less toxic than epinephrine and might counteract the vasodepressant effects of the carotid sinus reflex, it does not seem advisable because of the associated secondary vagal action on the heart (bradycardia and slowing of atrioventricular conduction¹⁹⁴). N-isopropyl-epinephrine (isuprel), on the other hand, stimulates the heart without elevating the blood pressure¹¹¹. It is capable of preventing carotid sinus-induced cardiac standstill and of accelerating ventricular action in the presence of complete block^{212, 213}. A combination of both substances might possibly be useful in a mode of application which would guarantee slow resorption and prolonged effectiveness.

Summary

The carotid sinus syndrome (bradycardia, atrioventricular block, cardiac standstill, fall of blood pressure, syncope, convulsions) is usually due to an intensified vagal reaction to mechanical pressure upon the pressoreceptor apparatus of the carotid sinus. Epinephrine prevents this reaction. A participating centrogenic derangement of sympathetic neurosecretory activity seems possible but has not been proven.

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A syndrome, consisting of dizziness, blurring of vision, pallor, faintness, sometimes leading to unconsciousness and convulsions of one-half to three minutes' duration, occurs in certain individuals upon turning or lifting the head, shaving, swallowing, wearing a tight collar, and in other conditions, connected with some degree of pressure on the neck. It was identified by Weiss and co-workers^{370, 3542, 3541} as the result of an abnormal sensitivity of the carotid sinus reflex mechanism. Attacks, identical with those occurring spontaneously, can be elicited in such patients by relatively gentle unilateral digital compression of the carotid sinus (4-40 seconds)^{370, 2420, 2463, 3542}. They are usually accompanied by vagal cardiac manifestations, such as retardation, atrio-ventricular block and cardiac standstill and there may or may not be a precipitous fall of the blood pressure. In some instances cardiovascular signs are minimal or absent, yet the subjective symptoms may be essentially the same, a fact which was ascribed to a presumable transient local vasoconstrictory ischemia of certain cerebral areas³⁵⁴².

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In some cases, a mechanical basis for an abnormal sensitivity of the reflex mechanism could be detected, such as aneurysmal dilatation of one or both sinuses, a compressing tumor or lymph glands^{2185, 3542} or an adjacent foreign body¹¹⁴⁰, but in others no anatomical abnormality seemed to exist. In some instances the seat of the functional disturbance, causing over-excitability or over-effectiveness of the reflex mechanism, may be located beyond the carotid sinus in the central synapses, the efferent neurons or even in the cardiovascular effector tissues, especially the heart itself²⁹³⁷. This is suggested by the fact that the syndrome, although altogether rare, occurs mostly in middle-aged or elderly persons with coronary sclerosis, with hypertension, and with damaged hearts^{3126, 3137} which are abnormally susceptible to vagal effects, leading to impairment of atrioventricular conduction and block⁴³⁶². In several cases, carotid sinus stimulation was seen to be followed by hemiplegia⁸² and in one by bilateral thrombosis of the anterior cerebral arteries²²²⁶, apparently as a result of the slowing of cerebral circu-

background, no definite information can be expected to evolve from available investigative techniques

Summary

Various patterns of fainting, usually associated with pallor, sweating, hypotension, and bradycardia, seem to originate in the brain itself (e.g., emotional) or to be elicited by peripheral reflex mechanisms. Gonadal function may exert an additional influence but no conclusive data regarding these points are yet at hand.

“Vasovagal” and Related Forms of Syncope

The term “vasovagal” syncope was introduced by Sir Thomas Lewis²⁰¹⁴ for the designation of neurogenic types of fainting, usually connected with pallor, sweating, a fall of blood pressure and bradycardia, and provoked by a variety of circumstances, such as physical pain, the sight of an accident or of surgical instruments, etc., and, especially in women, intense emotions, ranging from the grief over the loss of a beloved person to the enchantment over the performance of a crooner. Furthermore, such episodes may take place following excessively strenuous exercise, during spinal anesthesia, during convalescence from an acute infection, during an acute gastroenteritis, during an arterial puncture²³⁹⁴, during distention of the rectum, colon, duodenum or the vagina³⁶⁸, or after the loss of an amount of blood too small to produce a significant alteration of the cardiac output¹⁰⁶⁰, e.g., in 3 per cent²⁶¹⁷ and 4.2 per cent²³⁸⁶ respectively of two large groups of blood donors.

These forms of fainting are only rarely observed in the supine position and may be considered as being closely related to the syndrome of orthostatic hypotension, discussed on p. 330 ff. Their mechanism is poorly understood. Observations in animals were interpreted as indicating abnormal cerebral inhibitory responses to depressor stimuli, originating in peripheral pressoreceptor areas¹⁶⁴⁶. Studies in persons who fainted after the withdrawal of blood suggested a simultaneous constriction of the skin vessels and vasodilatation in the muscles under central nervous influence^{136, 137, 3503}. It seems possible that those specific sympathetic fibers which cause vasodilatation in the musculature under hypothalamic control^{452, 453, 1012} by mediation of still unidentified chemical transmitters^{452, 453}, are involved in the mechanism of fainting. In some cases, tachycardia occurs in the early phase of the syndrome²⁹³⁷. It is often followed by marked slowing of the heart rate; hence the term “vasovagal syncope”²⁰¹⁴. The feature of unconsciousness does not seem to be necessarily dependent on a profound alteration of the hemodynamic state, as it not infrequently precedes both the bradycardia and the hypotension of the vasovagal syndrome²⁹⁴⁷.

A certain loose relationship of some types of syncope with the endocrine system can be assumed in view of the relatively frequent occurrence of fainting in adolescents of both sexes, in menopausal women, during menstruation and pregnancy and after the stress period of infectious diseases. However, here, as in various other conditions with a questionable endocrine

(minutes to hours⁴⁰⁷) before permanent damage to the vasomotor centers develops^{437 2391}

Among the *neurogenic shocks of peripheral origin*, one may list those produced by injury to the upper sections of the spinal cord, by spinal anesthesia, by a blow to the abdomen, by abdominal surgery, by perforation of a hollow organ in the peritoneal cavity, by arterial puncture, and by some injuries producing intense pain. Here again we find an overlapping with the category of vasovagal syncope (see preceding chapter) with which the reflexory neurogenic types of shock have an early occurrence of arteriolar dilatation and pooling of blood in the periphery in common.

A situation quite different from the above-enumerated forms of neurogenic shock with vasodilatation exists in those shock syndromes in which the cardiac output declines^{1212 1082 1592}, owing to a loss of blood or plasma volume, as in the case of hemorrhage, of excessive diarrheas, vomiting and perspiration, of dehydration due to exaggerated urinary excretion of water and electrolytes, and of extravasation of blood or plasma into extensively traumatized or burned areas

These less abruptly developing forms of "secondary" shock whose onset may be delayed for a half hour to 12 hours or more⁴³⁷ after establishment of the causal disturbance, are characterized, like primary shock, by a diminished cardiac output⁶²¹ and a low blood pressure (average of one series 76/48 mm⁴⁴¹). The clinical appearance, too, may superficially resemble that of primary neurogenic shock, as far as pallor, the usually cold, moist skin, compressible pulse, general weakness and apathy are concerned. However, there are some significant points of distinction, such as cyanosis of the lips and nail beds, a dry tongue, indicative of dehydration, a greater tendency toward tachycardia (while in neurogenic shock the heart rate is often slow), non-responsiveness to lowering of the head, a longer duration of the shock^{441 442 443}

loss of either

the blood, especially in hemorrhage, occasionally hyperglycemia, and a reduced CO₂-combining power in case of dehydration with acidosis

The most important difference between the vascular state in primary and secondary shock, concerns the decrease of arteriolar tone (particularly in the somatic musculature) in the former and the general vasoconstriction prevailing in the latter^{1212 1082}. Accordingly, in secondary shock the diastolic pressure may remain within normal limits for some time or it may be diminished, but to a lesser degree than the systolic pressure which declines markedly on account of the reduced cardiac stroke volume.

Detailed studies of the circulatory changes in shock have been carried out by Courmand and co-workers⁴⁰¹ and others (lit., see ⁴³⁷). The blood flow through the kidneys was found extremely reduced^{1212 1082 1592}, while the

Shock

Definition and General Principles

The bodily derangements of neurogenic, traumatic, hemorrhagic, infectious, toxic, thermal or actinic origin, which are included in the collective designation "shock", share the outstanding common phenomenon of a more or less acute diminution of the cardiac output with resulting impairment of the oxygen supply to the tissues.

The following discussion will be limited to (a) those features of shock which can be assumed with some justification to be caused by a primary alteration of neurohormonal and hormonal function, and (b) to changes in the neuroendocrine and endocrine systems which develop as secondary features in various types of shock and which seem to contribute to the characteristic clinical manifestations of these shock patterns.

The terms "*neurogenic*" or "*primary*" shock are applied to significant reductions of cardiac output, caused by primary abnormal conditions in the central nervous system itself or provoked by primary peripheral changes which are associated with immediate nervous reflectory reactions on the part of the cardiovascular system. In a sense, the vasovagal syncope elicited by emotions, pain, etc. (see preceding chapter), and the syndrome of orthostatic hypotension (p. 330) may be looked upon as more or less closely related to primary or neurogenic shock.

Shock phenomena, resulting from injury or ischemia of the central vasomotor apparatus, were seen to occur in connection with traumatization of the brain, including cerebral surgery^{3025, 3416}, in less than 10 per cent of all cases⁶⁸⁷. Disorganization of central vasomotor control gives rise to peripheral vasodilatation and cardiac failure, sometimes accompanied by asphyxia due to concomitant lesions of the respiratory center, pulmonary edema^{212, 2390} and coma³⁰²⁵, ending in death. In other cases, a period of arterial hypotension and bradycardia may be followed by recovery⁷³⁹, or the cerebral trauma may precipitate more or less marked, sustained or periodical elevations of the blood pressure for varying lengths of time (p. 322).

Cerebral ischemia due to increased intracranial pressure or to a reduction of the circulatory blood volume may likewise lead to circulatory failure if anoxia of the cerebral and medullary centers progresses far enough to produce central vasomotor paralysis¹¹¹⁰.

Unless secondary shock (see below) or early death ensues, the manifestations of neurogenic shock subside as a rule after a limited period of time

the transition from one phase into the other. However, a word of caution against over-estimation of neurohormonal- and hormone-induced cardiovascular changes as the sole decisive factors in the clinical course of shock may be appropriate at the outset of the following review. Manifest metabolic alterations take place in the body as an accompaniment and aftermath of shock-producing injury and stress. We shall abstain from a discussion of this complicated and problematic field which has been extensively presented in Davis' monograph on "Shock"¹⁴² and in Selye's book on "Stress"¹⁴³.

The cardiovascular phenomena of primary "neurogenic" shock develop with great rapidity. They consist of a sudden preponderance of local vasodilatory action (particularly of the arterioles of the musculature) over the opposite effect of sympathogenic nor-epinephrine which is normally instrumental in maintaining the vascular tone, except perhaps under basal conditions and in the supine position¹⁴⁴. Certain sympathetic fibers which supply the vessels of the skeletal musculature elicit local vasodilatation under hypothalamic control^{141, 145, 146}. Despite some indirect evidence of a cholinergic activity of these fibers¹⁴², there still remains the possibility that their dilating effect upon the vessels of the musculature is caused by local discharges of epinephrine in contrast to the neurosecretion of constricting nor-epinephrine which characterizes most areas of the sympathetic system¹⁴⁷.

In a self-experiment, carried out by ¹⁴⁸ -
tion of 13 mg of epinephrine, the blood pressure fell to such a low level that measurement was not possible. A similar phenomenon was seen in a patient with Addison's disease after intravenous injection of epinephrine.

Small doses of epinephrine were found to dilate the arterioles of the limbs, while large ones had the opposite effect^{149, 150, 151}. Conversely, the splanchnic vessels were constricted by small doses and dilated by large ones¹⁴⁹. The dilating action of injected epinephrine was ascribed to a direct effect on the arteriolar walls by contact^{152, 153, 154}, to a hypothetical intracellular liberation of acetylcholine under the influence of ¹⁵⁵ -

liberation of acetylcholine by special vasodilator fibers¹⁵⁶. A central depression of vasoconstrictor tone¹⁵⁷ was also considered. The vessels of the skin¹⁵⁸, bones¹⁵⁹, spleen and kidneys on the other hand, were found to react to epinephrine regularly with constriction¹⁶⁰. Dihydrogenated ergot drugs are capable of "unmasking" the vasodilator component of epinephrine action by blocking the vasoconstrictor effect selectively¹⁶¹.

Proceeding on the assumption that an exaggerated dilating epinephrine

scantly innervated cerebral and coronary arteries which do not participate in the active vasoconstriction, receive a comparatively large amount of blood with the result that during this "compensatory" stage of shock the mental capacities are fairly well preserved. Electrocardiographic or other signs of anoxic cardiac damage are usually absent³⁶¹⁴.

Some teleologists eulogize this state of affairs as allegedly developing "in order" to protect the vital organs and to preserve the life of the individual. However, no such fanciful emphasis is given to the fact that in the vast majority of untreated cases the situation progresses inexorably into one of a quite different nature which supersedes the preceding phase "in order" to kill the individual, regardless of the personal desirability of survival. This latter potentially fatal development, which was designated as "irreversible shock" by Wiggers³⁶¹⁵, is characterized by a further fall of the blood pressure, probably due to failure of the vasomotor centers^{1568, 3618} and to myocardial weakness³⁶¹³. Cardiac involvement may be manifested by dilatation of the heart¹⁵⁰³ and by electrocardiographic changes, such as depression of the S-T interval, flattening or inversion of the T-wave, low voltage and auricular fibrillation^{412, 3990}. General tissue anoxia, resulting from the preceding stage of vasoconstriction and hypovolemia, and particularly ischemic damage to the liver¹¹²⁹, in conjunction with anoxic changes in brain and heart, have been made responsible for the development of the ultimate fatal phase of shock. The heart muscles of animals subjected to various types of prolonged shock, were found to display areas of fatty infiltration and necroses, suggestive of anoxic lesions²²⁹³.

Role of the Adreno-Sympathogenic Neurohormones

In view of the identity of sympathetic action upon the cardiovascular system with the functional effects, exerted by the sympathomimetic catecholamines, liberated at the sympathetic nerve terminals and discharged from the adrenal medulla, we shall tentatively consider the cardiovascular manifestations of the three phases of shock (primary, secondary, and irreversible) from the point of view of adrenergic neurosecretion and adrenal medullary activity, and of their interplay with other hormonal influences, especially on the part of the adrenal corticoids. As far as the latter are concerned, it will be recalled (a) that epinephrine (but not nor-epinephrine) promotes the discharge of ACTH via the hypothalamus and by direct action upon the anterior lobe, and (b) that the pressor effects of both nor-epinephrine and epinephrine are enhanced by the mineralocorticoids, probably through intracellular deposition of sodium, and weakened by adrenal cortical deficiency, probably through loss of intracellular sodium.

The realization of these neurohormonal-hormonal interactions should prove useful in the analysis of the individual phases of shock as well as of

the transition from one phase into the other. However, a word of caution against over-estimation of neurohormonal- and hormone-induced cardiovascular changes as the sole decisive factors in the clinical course of shock may be appropriate at the outset of the following review. Manifold metabolic alterations take place in the body as an accompaniment and aftermath of shock-producing injury and stress. We shall abstain from a discussion of this complicated and problematic field which has been extensively presented in Davis' monograph on "Shock"¹⁴⁶ and in Selye's book on "Stress"¹⁴⁷.

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Proceeding on the assumption that an exaggerated dilating epinephrine

action may be involved in primary neurogenic shock, we have to consider the question as to whether there exist any indications for an actual increase of epinephrine secretion by the adrenal medulla or by the post-ganglionic fibers or by both. Various animal experiments suggest an increased epinephrine discharge from the adrenal medulla during or following such conditions as anoxia^{859, 1543, 2672}, reduction of the blood volume³⁴¹⁹, traumatization of the intestines²⁶⁷², and other forms of shock^{199, 1016, 1049, 2741}. In the adrenal glands of humans who had succumbed to stress situations, the epinephrine content was found significantly decreased³⁴¹⁹. Most of these observations were carried out before the discovery of nor-epinephrine as the universal vasoconstrictor par excellence. They were looked upon as evidence for an active part played by epinephrine in giving rise to the general vasoconstriction, which is characteristic for the secondary shock phase rather than for the primary, neurogenic shock. It seems worthy of note, however, that in some of these experiments^{1049, 2741} the criteria for epinephrine discharges presented themselves at a maximum in the early stages of traumatization (one-half to two hours), i.e., in the period corresponding to primary "neurogenic" shock and vasodilatation, but receded again during the later stages. These findings as well as the production of circulatory failure by prolonged infusion of small doses of epinephrine¹⁰⁴⁶, do not furnish conclusive proof; but they are at least compatible with the hypothetical assumption that an abnormal discharge of epinephrine from the adrenal medulla or/and from the post-ganglionic sympathetic fibers, supplying large sections of the vascular tree, particularly in the musculature, contribute to the vasodilatory state of primary neurogenic shock. (This apparently mild epinephrine over-activity, involved in neurogenic shock, should not be confused with the so-called "adrenalin shock"¹⁶⁶⁷, resulting from large, highly toxic quantities of epinephrine and producing an increase rather than reduction of the plasma volume¹²³⁴ with pulmonary edema and cardiac dilatation⁶⁵⁷) In order to explain the seemingly paradoxical absence of the usual pressor effect of increased medullary epinephrine secretion, one has to consider the diminution of the cardiac output in neurogenic shock, as compared with its augmentation, otherwise elicited by epinephrine. Except in the case of immediate outward losses of circulatory fluid, it seems necessary to postulate a reduction of venous return to the heart which might be caused by a pooling of blood in the venous part of the peripheral circulation and by the loss of skeletal muscle tone. Besides, it is possible that vagal effects act simultaneously upon the heart¹⁶⁶⁷ in neurogenic shock which would prevent development of the full stimulating influence of circulating epinephrine upon cardiac dynamic action.

Whether or not the presumable increase of the dilating epinephrine action on the muscular and other arterioles in primary neurogenic shock is

paralleled by a diminution of sympathogenic nor-epinephrine discharges into the vascular walls cannot be decided at this time. In sympathectomized animals, experimental hemorrhage is followed by an earlier, deeper and more prolonged fall of the blood pressure than in primarily intact animals.^{108, 109} This seems to indicate that in the latter the sympathetic vascular tone is being partially maintained despite shock-producing conditions.

One feature of early shock, which appears to lend additional support to the assumption of an increased epinephrine activity in this stage, is the eosinopenia which was found to be induced by surgical trauma^{110, 111}, electroshock¹¹², exposure to cold temperature¹¹³, emotional stress¹¹⁴, etc., in analogy to the fall of the eosinophil count which follows the injection of epinephrine¹¹⁵ but not of nor-epinephrine¹¹⁶.

If and when the secondary, "compensatory" shock phase develops, either immediately subsequent to the neurogenic phase or separated from it by a period of apparent well-being, the circulatory situation becomes dominated by general vasoconstriction in contrast to the vasodilatation which prevails during primary shock. The term "compensatory" phase is used by some workers for this stage to indicate the maintenance of some degree of hemodynamic equilibrium in the face of hypovolemia, by means of increased vascular tonicity. Various theories have been advanced to explain this latter phenomenon. One possibility is an automatic preponderance of peripheral constrictor sympathetic tone (nor-epinephrine action), resulting from the sequence: hypovolemia—decreased venous return—decreased cardiac output—inhibition of the pressoreceptor vagal mechanisms¹¹⁷. Another ingeniously conceived and experimentally amply supported concept was based by Zweifach, Shorr and their co-workers¹¹⁸ on the assumption that two vasotropic principles (VEM and VDM) and their mutual balance determine the circulatory course of the shock syndrome. VEM, the vasoconstrictor principle, originating in the ischemic kidney of the shocked organism, sensitizes the mesenteric terminal arterioles and pre-capillaries to topically applied epinephrine and nor-epinephrine and thus produces an exaggerated locally constricting effect on these particular vessels. This phenomenon is assumed to contribute significantly to the general state of vasoconstriction, although the validity of the findings obtained on the mesenteric vessels has not yet been proven for other vascular areas. VDM, the antagonistic vasodepressor material (chemically identical with *formyl- α -methyl- β -alanine*

... on the response of the mesenteric vessels to topical epinephrine, and its thus indirectly relaxing action on parts of the vascular system is believed by Shorr and associates¹¹⁹ to

replace more or less gradually the vasoexcitor activity of VEM. The blood pressure falls further (abdominal pooling of the already reduced circulatory volume) and transfusions remain ineffective in this now established *phase of irreversible or "decompensatory" shock*. The simultaneous weakening and final disappearance of the pressor effect of injected epinephrine^{637, 2502} may correspond to a preponderance of VDM activity at this stage and support the above-reviewed theory. Sympathectomy¹⁰⁶¹ and the sympatholytic drug dibenamine³⁶¹³ were shown to prevent the general vasoconstriction of secondary shock and its hypoxia-induced progression into the decompensatory phase.

Role of the Pituito-Adrenocortical Axis

Recognition of the mutual relationship between the pituitary gland and the adrenal cortex and of the fundamental involvement of their functions in the "alarm reaction"³⁰⁷⁷ has focused considerable interest on the reparatory as well as pathogenic role, played by pituitary and adrenocortical responses to stress and their significance for the development of the various phases of shock.

The demonstrable criteria for alterations in adicnal cortical structure and activity, resulting from stressful situations, can be divided in (a) chemical and morphological changes of the cortex, (b) functional manifestations (blood eosinophil and lymphocyte count, electrolyte-) and (c) hormone excretion in the urine

Morphological changes of the adrenal cortex, such as a loss of sudanophilic lipids, hyperemia, hemorrhages, leukocytic infiltration and necroses, especially in the zona fasciculata, have been observed in animals and humans after such stresses as anoxia¹¹³⁴, freezing²³⁹³, burns³¹⁷, traumatization^{779 3439}, hemorrhage²⁴³, and dehydration⁶⁹². A diminution of cortical cholesterol and ascorbic acid, analogous to that produced by injection of ACTH and indicative of an intensified cortical secretory activity, occurs with great regularity as a sequel of stresses and injuries of all kinds^{1372 2042 2091, 2935 3439}.

Functional evidence for an increased glucocorticoid secretion under stress was deduced from the fall of the eosinophil^{42 1602 1679 2324 2395} and lymphocyte counts^{34, 617 2121 1375, 1599 2395} in the blood after traumatization and in other stressful and shock-inducing conditions, as well as after injection of epinephrine²⁷⁵⁵.

An increase of mineralocorticoid action under the influence of stress is suggested by a retention of sodium and elimination of potassium which was observed in humans after surgical interventions^{573 2549} during the compensatory phase, while a decrease of the blood chloride level may occur in the later shock phase³⁰⁷⁴.

An augmented excretion of corticoids in the urine was observed after surgical operations^{1914, 2175, 2239} burns and in infections²¹²².

Thus, an exaggeration of adrenal cortical secretory activity appears firmly established as a feature of the shock syndrome and we have now to examine the questions as to which element, common to all forms of stress, sets the pituito-adrenocortical secretory mechanism into motion, what makes it proceed either to renormalization or to ultimate failure, and what is the significance of these hormonal upheavals for the clinical course of shock.

The well-known stimulating effect of epinephrine upon the pituito-adrenocortical system (evidenced by the eosinopenic reaction²²⁹¹ and by secondary chemical changes in the adrenal cortex^{229, 2917}) on one hand, and the increased epinephrine discharges which occur during the early "neurogenic" phase of stress situations on the other, make it probable that epinephrine acts as an initiating factor in the sequence of hormonal changes accompanying shock. However, in Sayers'²²⁸² words, it is still uncertain whether epinephrine is "a necessary and essential link in the series of events which lead to increased secretion of cortical hormone during stress or whether epinephrine acts like other non-specific stresses to increase the needs of tissues for cortical hormones". Selye²⁰⁷⁷ expresses himself even more cautiously by stating that it is not known in which way trauma to tissues acts on the pituitary to stimulate the adrenal cortex, whether nervous or blood-borne stimuli to the hypothalamus and pituitary are responsible for the subsequent developments. Be that as it may, unless recovery and return of the exaggerated adrenal cortical function to normalcy take place, sooner or later a stage will be reached at which cortical steroid production will decline until signs of adrenal cortical insufficiency supervene. The progression to this ultimate stage is probably caused not only by depletion of the cortical hormone reserves but also by the inhibitory effect which the circulating corticoids of the hypersecretory phase exert themselves on the pituitary gland, thus indirectly suppressing a further adequate release.

The comparison of various details of the shock syndrome and to make death from shock appear as one, essentially due to adrenal cortical insufficiency. The fact that both hypophysectomy²²⁹ and adrenalectomy^{207, 227} greatly decrease the resistance to shock appeared to be consistent with this concept. Nevertheless, it is felt that

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the low blood sugar level of hypoadrenocorticism, as contrasted with the

sugar, increase of urine secretion and a rise of the blood pH to near the value of 7.42.

Despite the profound involvement of cardiovascular abnormalities of partly neurohormonal and hormonal origin in the shock syndrome, as discussed in the preceding sections, the practical therapeutic applicability of the information gathered in this domain has proved disappointingly meager up to the present.

Probably the most efficient measure to be taken against the vasodilatory diminution of venous return to the heart in primary neurogenic shock is still the time-honored primitive trick of putting the patient into the so-called shock position with the head at a lower level than the feet. Vasoconstrictor agents of the sympathomimetic group, such as paredrine and neo-synephrine, were used with some success in neurogenic shock after hemorrhage and trauma and especially in shock which was induced by spinal anesthesia.^{1099 1461 2243} According to a recent report¹¹⁷⁶, nor-epinephrine may prove the drug of choice for both neurogenic and early hemorrhagic shock conditions, administered by intravenous infusion of 0.1-0.3 micrograms/kg/minute.

Opinions regarding the efficacy of adrenal corticoids in the prevention and treatment of experimental shock are contradictory but with the stronger evidence supporting the negative side. Statements claiming a favorable influence of adrenal cortical extracts and DCA in clinical shock^{296 1132 1625 1749 2579 2629} were not confirmed by other workers.^{229 245 457 1725 2092, 2749, 2830} DCA proved ineffective in preventing surgical shock¹⁴²⁵ and adrenal cortical extract in influencing shock from burns²⁷⁴⁶ in human beings. These facts suggest strongly that shock-induced adrenal cortical insufficiency does not play a dominating role in the course of the shock syndrome, except possibly in infections and certain toxic conditions. This does not apply, of course, to the special case of the shock-like manifestations of Addisonian crises (p. 112) nor to the shock situations which occur following removal of adrenal tumors. In these cases, both adrenal corticoids and epinephrine (probably also nor-epinephrine) are of great therapeutic value (p. 88, 101 ff.).

Pitressin in subpressor doses was found in animals to postpone death from irreversible shock for a few hours²²³⁴, but a usefulness of posterior lobe extracts in clinical shock has not yet been demonstrated.

Summary

The outstanding feature of all forms of shock is a marked diminution of the cardiac output, either due to an outward loss of part of the circulatory fluid volume or to a faulty distribution of the latter, resulting in a diminished venous return to the heart.

The three phases of the shock syndrome, which are distinctly discernible

normal or elevated blood sugar in shock, and the different responses to administered corticoids. The therapeutic use of cortical extracts is by far not as effective in preventing or abolishing the final phase of shock as one would expect if the latter were essentially caused by cortical insufficiency alone and by no other equally or more important factors.

Despite the apparent limitations of the pathogenic role of pituito-adrenocortical derangements in the shock syndrome, these hormonal changes are nevertheless undoubtedly of great contributory significance. Little is yet known about their direct influence on cardiovascular function, but judging from the enhancing effect of adrenal corticoids upon adrenosympathogenic pressor action and from the opposite situation in cortical deficiency, it does not appear unlikely that the general vasoconstriction in the second shock phase and the vascular hypotension and non-responsiveness to sympathomimetic stimuli in the "decompensatory" stage of irreversible shock, may be in part attributable to adrenal cortical hyper- and hyposecretion respectively.

Treatment

In accordance with the wide range of shock-precipitating conditions and of shock manifestations of all grades, there are no rigidly established rules regarding the treatment of shock, except for the basic principle that augmentation of the reduced cardiac output is the primary and ultimate goal to which all other therapeutic measures have to be subordinated. In the great majority of cases in which the circulatory fluid is diminished, especially in hemorrhagic and traumatic shock, but also in other instances of extravasation and dehydration, the restoration of the circulating volume through infusions of adequate amounts of whole blood, plasma, saline and glucose solutions or various synthetic solutions, such as Dextran or Periston, is of paramount importance. These infusions have to consist of one or several liters but must be given with caution in individuals with damaged hearts or with oliguria in order to avoid cardiac failure and pulmonary edema. It would transcend the scope of this review to elaborate on the detailed indications and technicalities of the infusions and of other therapeutic procedures which are not directly related to our subject. The maintenance of an appropriate environmental temperature, the administration of oxygen, analeptic drugs, etc., and the various measures directed against underlying morbid conditions of a traumatic, surgical, infectious, toxic nature, etc., are thoroughly discussed in Davis' "Shock"^{16,17} and other special publications.

Objective criteria of clinical recovery from shock consist of a return of the pulse pressure and blood pressure toward normal, restoration of mental alertness, normalization of urea nitrogen, non-protein nitrogen and blood

Neurocirculatory Asthenia

Definition and General Principles

The protean symptomatology of what is usually referred to as "neurocirculatory asthenia", "effort syndrome", "irritable heart", "neurasthenia" or "anxiety neurosis" has been well known to physicians and laymen alike for ages past. In 1871, it was described in detail by DaCosta⁶¹, but systematic attention was concentrated upon it only after the first World War when Sir Thomas Lewis devoted to it his famous monograph *The Soldier's Heart and the Effort Syndrome*⁶². With increasing realization of its widespread occurrence and of its practical significance in both civilian and military life, and with the advent of the "psycho-somatic" schools of thought, it became the object of extensive physiological and psychological studies, intermingled with some psycho-somatic star-gazing.

The somewhat indistinctly circumscribed syndrome of neurocirculatory asthenia embraces a wide range of unpleasant and sometimes distressing sensations, among which cardiovascular symptoms are characteristically prominent. They are described by Wendkos³² in condensed terms as a labile blood pressure with the systolic level more variable than the diastolic, and a labile pulse rate which tends to be raised during working hours but normal during sleep. Less regularly occurring symptoms of directly or indirectly cardiovascular origin are: palpitations, cold clammy hands, flushing of face and neck, headaches, faintness and even syncope. Others, such as a dull or stabbing precordial pain and often marked shortness of breath, mostly in connection with physical exertion and emotional excitement, although frequently misinterpreted as indicating cardiac pathology, have to be considered as independent neurogenic phenomena of probably hypothalamic derivation³⁰². The same applies to such additional phenomena as fatigability, general weakness, giddiness, irritability, apprehensiveness, sometimes reaching the proportions of outright attacks of anxiety, claustrophobia, indigestion, anorexia, slight elevations of temperature, axillary perspiration, tremors, shakiness, paresthesias and insomnia (lit., see ⁶¹, 171).

Neurocirculatory asthenia rarely makes its appearance before the 18th year⁶¹ or after the onset of old age. A clear differentiation from the menopausal syndrome is not always possible. Its occurrence in a series of civilians has been estimated as 5.6 per cent³³, with the number of women about twice that of men⁶³, but during war time and under the stress of other mass catastrophes, the incidence is likely to attain much greater proportions¹²⁰.

in some cases while they develop only incompletely or merge imperceptibly in others, are designated as (1) the primary "neurogenic" phase (transitory vasodilatation and blood pooling in the periphery), (2) the secondary "compensatory" phase (peripheral vasoconstriction), (3) irreversible "decompensatory" shock (vasomotor paralysis).

Neurohormonal factors seem to be involved in the neurogenic phase insofar as abnormal medullary and/or neural discharges of epinephrine, unassociated with an adequate cardiac output, may be suspected of exerting a prevaillingly dilating action upon the arterioles, especially of the musculature. The adrenal cortex is not significantly involved in this phase as a pathogenic factor.

In secondary shock, a high "compensatory" vascular tonus is established in the periphery, probably as a result of reflexes from pressoreceptor vascular areas, which may cause a prevalence of constrictor nor-epinephrine effects at the sympathetic vascular nerve terminals. Furthermore, the mesenteric vessels may be sensitized to local vasoconstrictor action of epinephrine and nor-epinephrine by an unidentified substance (VDM), which originates in the ischemic kidney. A concomitant stress-induced increase of adrenal cortical secretion may conceivably act as an additional supporting factor in maintaining a high vascular tone.

The development of the final "decompensatory" phase appears to be precipitated by a supervening paralysis of the ischemic vasomotor centers, weakness of the anoxiated heart, exhaustion of the adrenal functional reserves and the liberation of VDM (ferritin) from the ischemic liver and muscles, which may contribute further to vascular relaxation and may cause non-responsiveness to vasoconstrictor stimuli.

Due to the only partial responsibility of neurohormonal and hormonal factors for the clinical course of the shock syndrome, the preventive and therapeutic usefulness of hormonal agents is a very limited one, perhaps with the exception of nor-epinephrine in the early, neurogenic phase.

physical rest by a low tidal air⁵⁴⁶ 1672, sighing spell^{551, 2002} and sudden attacks of tachypnea and dyspnea of an apparently primary central origin. They are unaccompanied by any objectively demonstrable impairments within the cardiorespiratory system¹⁶⁷². The breath-holding capacity is diminished⁵⁵² 2050 and the resistance to CO₂-rebreathing is reduced⁵⁵¹. On this basis, a combined hyperventilation and breath-holding test has been devised for the differential diagnosis of neurocirculatory asthenia against organic cardiorespiratory diseases¹⁶⁷².

The endurance for physical work is markedly diminished⁵⁴⁷ and strenuous exercise is accompanied by an abnormal increase of the blood lactate concentration⁵⁴⁸ while oxygen consumption remains comparatively low during work⁵⁴⁴ and afterward¹⁶⁷¹. From these peculiarities, an increase of anaerobic metabolism was concluded⁵⁴⁷. The basal metabolic rate was found within normal range²⁴⁴⁸, a fact which is important in distinguishing the syndrome of neurocirculatory asthenia from thyrotoxicosis.

Neurohormonal and Hormonal Aspects

The nature of the cardiovascular abnormalities in neurocirculatory asthenia has long been recognized as the expression of an "autonomic imbalance"¹¹⁷⁴⁰. In terms of present-day knowledge of the functions of chemical neurotransmitters of the autonomic nervous system, one has to consider the problem as one of an apparent imbalance between adrenergic (nor-epinephrine, epinephrine) and cholinergic (acetylcholine) neurosecretion. In view of the apparently outstanding causative role of cerebral cortical and hypothalamic functional manifestations in the syndrome, it may be permissible to insert a hypothetical remark about a conceivable involvement of enkephalin, an epinephrine-like amine with pressor, cardiac stimulating, pupillary dilatatory and other sympathomimetic properties (Figs. 43, 46, 47), which was found in relatively large amounts in the cortex and stem ganglia of the brain of various mammalian species, including homo sapiens²⁶⁴³ 2694. Nothing is yet known about the physiological significance of this potent substance but it would seem surprising if it would not actively participate in the central neurovegetative functional regulations.

A prevalence of *sympathogenic cardiovascular effects* in the majority of neurocirculatory asthenic patients has been stressed by several workers¹⁰⁷² 1224 1291. It is suggested by the tendency toward tachycardia and transitory elevations of the blood pressure, by directly observed phenomena of vasoconstriction¹⁰⁷², and by the analogies of various clinical features of the syndrome with those of thyrotoxicosis⁵⁵³ 2092 and of nicotine intoxication¹²⁹¹. Furthermore, the syndrome presents conspicuous similarities with the effects of injected

In the individual case, the syndrome is usually precipitated by identifiable situations, creating more or less justified feelings of insecurity and frustration. A marked accentuation of the symptoms occurs in connection with strenuous physical exertion, such as demanded by the exigencies of military service, and by the victimization of civilian populations pertaining to modern warfare. Under such conditions, the disease may develop acutely and temporarily in otherwise unafflicted individuals. Infections and malnutrition may likewise act as causative factors but a background of emotional instability can be assumed to be involved also in these instances. A hereditary disposition was ascertained by several investigators^{557, 2450, 3667}. Claims regarding a prevalence of neurocirculatory asthenia among certain constitutional types of body build have not been substantiated^{1291, 3563}.

In sharp contrast to the subjective fears of the patients suffering from neurocirculatory asthenia, the prognosis *quoad vitam* is a decidedly favorable one⁵⁵¹, no matter how intense the discomfort. The percentage of actual complete recoveries, on the other hand, is low (13.3 per cent in a 20-year follow-up of 173 cases⁵⁵¹). In accordance with the emotional factors involved, the intensity of the symptoms varies with the fluctuations of the precipitating outward conditions. It seems of particular interest that a progression into frank essential hypertension is apparently not specifically induced by the state of neurocirculatory asthenia^{406, 943}. Except in cases with independently coexisting cardiovascular diseases, the objective findings of heart size^{176, 1072} and electrocardiogram at rest³⁶⁰⁰ do not differ characteristically from those obtained in the general population. Occasional instances of a small heart^{2250, 2271} and of electrocardiographic abnormalities^{1241, 2075, 2249, 2563} cannot be considered as specific for the syndrome of neurocirculatory asthenia, even though states of anxiety are capable of eliciting alterations of the T-wave^{2082, 2191}. The heart rate may be elevated also at rest^{603, 3600}.

More significance is to be attached to the cardiovascular reactions, occurring in patients with neurocirculatory asthenia during and after exercise and in other acute states of stress. Excessive rises of the pulse rate and an abnormally slow return to normal were observed in connection with various working tests^{351, 557, 598, 3539} and following application of intense light and sound stimuli²²⁷². Electrocardiographic abnormalities, including extratricular extrasystoles and conduction disturbances, were recorded immediately and up to six minutes following exercise tests in 18 per cent out of 1650 soldiers with normal resting electrocardiograms¹⁹²⁵.

Overshooting blood pressure reactions to muscular work were likewise observed in persons with neurocirculatory asthenia^{598, 1291}, but the cold pressor test gave normal results in one series of cases⁴⁰⁶.

The often distressing respiratory symptoms, although markedly aggravated by exercise and emotions, may be distinctly manifested also at

by the action of adrenosympathogenic catecholamines upon the heart muscle and the vascular tree. In a minority of instances, signs of apparent vagal preponderance were occasionally observed, such as an abnormally deep fall of the blood pressure after exercise and in the erect position, but it seems doubtful that such cases belong in the category of neurocirculatory asthenia, as defined above¹²⁹¹. It was not found possible to reproduce an exacerbation of the characteristic symptoms of neurocirculatory asthenia by application of cholinergic drugs¹⁰⁷².

Significant parallels exist between the effort syndrome and the reactions of healthy but untrained individuals to exceptional physical strain¹⁰⁷. Comparing the extremes of a flabby, sedentary intellectual, haunted by problems and worries on the one hand, and a highly trained athletic muscle man with a minimum of cerebral extra function on the other, one is likely to find the signs of jittery sympathetic over-activity in the former and of calm vagal preponderance with almost imperturbable bradycardia in the latter. One gains the impression that it is not so much an absolute increase in adrenergic neurohormonal discharges which besets the neurocirculatory asthenic individual rather than a deficiency of those cholinergic vagal counter-reactions which maintain homeostasis in the normal person, and which are developed to an overwhelming maximum in the professional athlete¹²⁹¹.

The possibility of an abnormal epinephrine-*nor*-epinephrine ratio with preponderance of the former is brought to mind by the observation that the adrenal medulla of aggressive, hunting animal species produces prevalingly the invigorating *nor*-epinephrine while that of non-aggressive "runners" produces predominantly the anxiety-creating epinephrine¹²⁹⁴.

No definite relationship of neurocirculatory asthenia to other endocrine glands can be claimed with any degree of certainty. Yet, the facts that the syndrome hardly ever occurs before the age of sexual maturity, that under normal conditions females are more frequently afflicted than males, and that there are fleeting transitions leading toward the menopausal syndrome, hint at certain apparent influences on the part of the gonadal steroids, probably acting primarily upon the central emotional and neurovegetative apparatus.

Treatment

In view of the fact that in the majority of cases the syndrome of neurocirculatory asthenia seems to be based on deep-rooted cerebral structural and coordinative patterns, there is little reason to hope for possibilities to modify radically its fundamental individual predisposition. The pressures of outward circumstances are usually beyond control by the treating physician, but his reassuring personal approach to the patient and to his

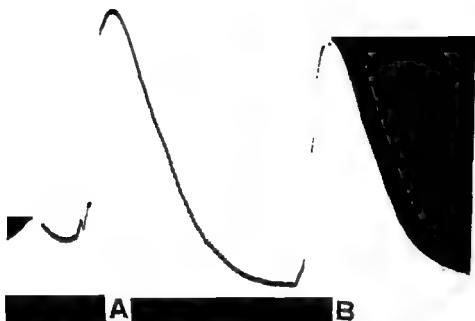


FIG 45 Effects of (A) encephalin (8 gamma equivalents, colorimetrically determined) and of (B) epinephrine (8 gamma) upon the blood pressure of the atropinized cat with the adrenals tied
(After W Raab, *Am J Physiol* 152 324, 1948)

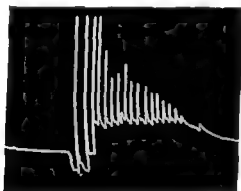


FIG 46 Effect of 2 gamma equivalents of encephalin upon the isolated rabbit heart which had come to a standstill
(After W Raab, *Am J Physiol* 152 324, 1948)



FIG 47. Effect of equipressor doses of epinephrine (B) and of human encephalin (C) on the pupil of the cat with the cervical sympathetic cut (A)
(After W Raab, *Am J Physiol* 152 324, 1948)

Regulatory Disorders of Peripheral Circulation

Definition and General Principles

In the origin of the peripherally vasoconstrictory or vasodilatory disturbances to be discussed in the following, the involvement of an abnormal function of the autonomic vascular nerves, especially the sympathetic, is suspected and a participation of other endocrine factors may also be considered with more or less justification.

Transient or prolonged spastic constrictions of the arterioles, without or with venous stagnation, occur in the digits or larger areas of the extremities, rarely also on the ears and nose, with resulting local pallor or cyanosis, coolness, paresthesias, pain and ultimately trophic lesions, ending in the severe forms in gangrene and loss of tissue. Cold temperature, mechanical factors, nervous reflexes, local inflammatory changes and emotional instability serve as originating mechanisms of the spastic vascular reactions. Another group of abnormal peripheral vascular reactivity manifestations is characterized by vasodilatation, redness, sensitivity to warmth, and burning pain, but not by trophic alterations.

Raynaud's phenomenon Individual attacks begin usually with blanching of the fingers and sometimes of the toes, due to tight constriction of arterioles and minute vessels, followed by cyanosis and subsequent erythema, when arteriolar flow is restored. Women are more frequently affected (most commonly in the third and fourth decades), but the disease occurs also in men. Primary structural lesions of the vessels do not seem to be prominent, although such claims have been made²⁰⁹. For the distinction of instances without and with organic vascular changes, the terms "Raynaud's phenomenon" and "Raynaud's disease" respectively have been suggested²¹⁰.

Whether similar vascular phenomena accompanying *scleroderma* are of an analogous primary vasospastic nature or initiated by the periarterial proliferation of collagen, which is specific for *scleroderma*²¹¹, has not been definitely decided. Structural abnormalities which were observed in the regional sympathetic ganglia²¹² may suggest the first-named alternative.

The so-called *scalenus anticus syndrome* is due to a compression of the subclavian artery and the brachial plexus by an adjacent hypertrophic

problems with common sense, genuine sympathy and encouragement, instead of useless medication and pampering, may achieve a great deal in building up the patient's morale and confidence in his ego and ability to overcome seemingly unconquerable obstacles. A gradual training for a reasonable degree of physical fitness without competitive ambitions should contribute to an improvement of vagosympathetic equilibrium.

Before the prescription of any medications is contemplated, it is well to scrutinize the psychological pros and cons of any measures which might on the one hand offer the patient some direct physical benefit but which might, on the other hand, unnecessarily consolidate his mental concentration on his illness. It does not make too much difference whether preparations without or with some pharmacologically or endocrinologically rational connotations are administered, such as ergot drugs, sedatives, analeptics or estrogens. The personality of the physician, his human understanding, psychological skill and cultural horizon are more decisive for success or failure than his prescription pad.

Summary

The syndrome of neurocirculatory asthenia can be considered as the neurovegetative corollary of a partly hereditary, partly acquired personality pattern whose somatic manifestations are brought to the fore or are aggravated by conditions which create feelings of insecurity and frustration. The cardiovascular symptoms, such as tachycardia, heart consciousness, palpitations and lability of the blood pressure, indicate an exaggerated prevalence of adrenergic sympathetic effects, especially under unaccustomed muscular and emotional strain. Some loose connections seem to exist with gonadal function and its influences upon the central nervous system. The prognosis regarding longevity is good; that for recovery, poor. Treatment has to proceed mainly on psychotherapeutic lines.

their mutual interplay, as well as that with histamine and possibly some other unknown vasoactive substances. Since practically nothing is known about these fundamental details, we have to limit the discussion of pathogenic factors to what little can be concluded from the circumstances under which the various above-mentioned peripheral vascular syndromes occur, and from some clues furnished by the results of specific forms of treatment.

The unquestionable dependence of at least some patterns of Raynaud's phenomenon on emotional stimuli points clearly toward the participation of central nervous mechanisms in these cases. This had been suspected by Raynaud himself as early as 1862²²⁷. It seems that even physiological central stimuli elicit abnormally intense constrictory responses of the vascular walls²²⁸ to locally acting neurohormones. No specific structural abnormalities could be detected in the sympathetic ganglia supplying affected vascular areas¹⁰⁰² but such changes have been described in cases of scleroderma²⁶⁴.

It is interesting to note that exposure of various parts of the body to abnormal temperatures was found to be accompanied by reflexory vasoconstriction in distant sections of the vascular system¹¹⁹, e.g., in the hand and arm^{244, 274}, and that even the anticipation of such thermal stimuli can evoke narrowing of peripheral vessels⁴⁴. Extraneous local thermal factors are so conspicuously involved in the precipitation of the symptoms of Raynaud's disease, and also of acrocyanosis, erythromelalgia, and others, that an abnormal direct sensitivity and reactivity of the vascular cells to cold or warm temperature respectively^{2016, 2017, 224} is believed by some workers to constitute another outstanding feature of some of these derangements. This latter conception seems to be supported by the fact that vaso-pastic attacks were seen in some instances to continue after sympathetic denervation^{2019, 2022}. The role of spinal vasodilator mech-

of the vasoneuroses, such as the prevalence of Raynaud's disease, scleroderma and acrocyanosis in women, of erythromelalgia and of the vaso-spasms accompanying thromboangitis obliterans in men, suggests some obscure connections with gonadal steroid activity. A tendency of acrocyanosis and of "dead finger"¹¹⁰⁰² to occur with particular frequency in girls at the age of pubescence or in menopausal women, and of erythromelalgia in men on the verge of senility, may be based on similar relationships. The occasional occurrence of Raynaud-like phenomena in patients with Addison's disease²⁰⁰⁸ and of acrocyanosis in cases of acromegaly¹⁹⁰² is probably of lesser significance concerning the question of a general hormone.

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portion of the scalenus anticus muscle near its attachment to the first rib or to a cervical rib^{14, 3235}. These mechanical factors are essentially responsible for the occurrence of coldness, blanching, cyanosis and lancinating pains in the hands, atrophy of palmar muscle groups, swelling and sometimes also digital gangrene¹⁸³².

Pneumatic hammer disease or *stonecutter's disease*, caused by the prolonged impact of vibrating tools, *crutch trauma* and *traumatic arteriospasm* following the healing of a fracture or penetrating wound of an extremity, are likewise characterized by periods of coldness, cyanosis, paresthesias and pain (*causalgia*) in the affected regions.

Functional arterial constrictions are frequently seen as aggravating complications of obliterating or embolic occlusive vascular disorders, such as peripheral arteriosclerosis and thromboangiitis obliterans (lit., see ¹⁸³²); but there exist also rare idiopathic forms of *painful arterial spasms* in the arms or legs with or without arteriosclerosis, occurring in all age groups and in some cases developing into symmetrical gangrene in the absence of any demonstrable participating cause²⁰¹⁷.

Abnormally vasodilatatory disorders concern the arterioles and capillaries or the superficial venules. The terms *erythromelalgia* and *thermelalgia* indicate conditions of increased surface temperature of one or both lower extremities with or without bright red discoloration of the dry skin, accompanied by pain which is markedly intensified by warmth, by walking, and by keeping the feet in the dependent position. The arterial pulsations of the lower extremities are lively, they show an increased oscillometric index and the arteriovenous oxygen difference of the foot vessels is greatly diminished, especially during the acute painful attacks^{293, 3171}.

Acrocyanosis appears as a persistent, dusky, sometimes mottled discoloration of the upper, and less frequently also of the lower extremities with some coldness, perspiration and occasional paresthesias. It is usually aggravated by exposure to cold temperature and during the winter season. The subpapillary plexus are dilated but it has been claimed that the arterial limbs of the capillaries are constricted^{835, 3021}. The condition does not lead to any major discomfort or serious complications.

Neurohormonal and Hormonal Aspects of Pathogenesis

For an appraisal of the pathogenesis of the peripheral, presumably neurogenic circulatory disturbances, it would be necessary to possess adequate information regarding the finer mechanisms of neurosecretory discharges of sympathomimetic catecholamines and acetylcholine into the vascular effector cells, their local fate under the influence of cellular enzymes, and

their mutual interplay, as well as that with histamine and possibly some other unknown vasoactive substances. Since practically nothing is known about these fundamental details, we have to limit the discussion of pathogenic factors to what little can be concluded from the circumstances under which the various above-mentioned peripheral vascular syndromes occur, and from some clues furnished by the results of specific forms of treatment.

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It is interesting to note that exposure of various parts of the body to abnormal temperatures was found to be accompanied by reflexory vasoconstriction in distant sections of the vascular system¹¹⁹, e.g., in the hand and arm^{64, 271}, and that even the anticipation of such thermal stimuli can evoke narrowing of peripheral vessels⁶⁴. Extraneous local thermal factors are so conspicuously involved in the precipitation of the symptoms of Raynaud's disease, and also of acrocyanosis, erythromelalgia, and others, that an abnormal direct sensitivity and reactivity of the vascular cells to cold or warm temperature respectively^{208, 201, 214} is believed by some workers to constitute another outstanding feature of some of these derangements. This latter conception seems to be supported by the fact that vasospastic attacks were seen in some instances to continue after sympathetic denervation^{202, 207}. In erythromelalgia, a causal role of spinal vasodilator mechanisms was considered as participating¹⁸².

The peculiar sex distribution of some of the vasoneuroses, such as the prevalence of Raynaud's disease, scleroderma and acrocyanosis in women, of erythromelalgia and of the vasospasms accompanying thromboangiitis obliterans.

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It is interesting to note that the age of onset of Raynaud's disease, of erythromelalgia and of the vasospasms accompanying thromboangiitis obliterans at the age of pubescence or in menopausal women, and of erythromelalgia in men on the verge of senility, may be based on similar relationships. The occasional occurrence of Raynaud-like phenomena in patients with Addison's disease²⁰⁸ and of acrocyanosis in cases of acromegaly¹⁸² is probably of lesser significance.

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induced syndromes, in the crutch syndrome and in the traumatic causalgia¹⁷⁷³, are indicative of states of abnormal irritation of post-ganglionic sympathetic fibers^{2017, 3211} which may be suspected of leading to intensified neurohormonal discharges by the sympathetic terminals. Physiological studies of the effect of epinephrine^{2391, 2534, 2759} and of acetyl-beta-methylcholine²³⁵¹ with the capillary microscope revealed constriction and dilatation respectively of the minute vessels.

Neurohormonal and Hormonal Aspects of Treatment

No attempt will be made here to discuss the manifold physical, mechanical, surgical, psychotherapeutic and other forms of treatment for the peripheral vascular circulatory derangements, which are not directly aimed at the supposedly underlying neuroendocrine and hormonal mechanisms.

As far as the latter are concerned, various techniques of *sympathetic surgery*, especially pre-ganglionic sympathectomy^{3174, 3361} have proved at least partially and temporarily successful in Raynaud's disease^{13, 135, 141, 3549}, scleroderma^{1432, 3390}, traumatic arterial spasm^{1565, 3132, 3590} and regarding the spastic component of thromboangiitis obliterans^{13, 3590}. In scleroderma the results of surgical intervention on the sympathetic system are probably least satisfactory³³⁶³. Recurrences of the spastic episodes after sympathectomy in Raynaud's disease have been ascribed to an increased epinephrine sensitivity of denervated structures^{3132, 3549}. Paravertebral sympathetic block was found useful as a diagnostic procedure to identify, to some extent, the degree of vasospastic involvement in occlusive arterial diseases. In arterial embolisms it relaxes the reflectory vascular spasm surrounding the embolus¹⁰⁹³.

Sympatholytic drugs, especially the dihydrogenated ergot alkaloids (DHO-180, DCS-90, DHK-135, CCK-179) which are free of the toxic muscletropic side effects of the ordinary ergot preparations²⁹⁷⁹, have been applied in vascular disorders with irregular results. Marked improvements were reported in 63 per cent of a series of 67 cases, comprising Raynaud's disease, acrocyanosis, traumatic circulatory lesions, and other vasospastic conditions¹⁷⁰¹. Partial improvement was obtained with these drugs also in occlusive arterial diseases^{1701, 2626}. Priscoline was found even more effective in angiospastic conditions^{1161, 2050a, 2626}. Tetraethylammoniumchloride and bromide are sometimes useful in Raynaud's disease^{244, 1161, 2029, 3174} and as differential diagnostic aids for the recognition of vascular spasms. They do not appear suitable for prolonged therapy, however¹¹⁶¹.

Mecholyl, applied either orally or by means of iontophoresis¹⁸³⁷, has been recommended for Raynaud's disease, the scalenus anticus syndrome and similar abnormalities.

Thyroid hormone may help to alleviate acrocyanosis¹⁸⁰² and scleroderma^{1812, 1803}. The latter condition was dramatically improved in one instance by the administration of dihydrotachysterol¹⁸¹⁰ while for other such cases partial parathyroidectomy has been advocated¹⁸¹¹. Patients, suffering from erythromelalgia are supposed to benefit from epinephrine injections¹⁸¹¹. Temporary normalizations were achieved in a few cases of Raynaud's disease with ACTH¹⁸¹³.

Summary

Peripheral arteriolar and capillary spasms, transient or prolonged, causing discoloration, coldness, pain and eventually trophic lesions, occur as the result of abnormal regional sympathetic stimulation (and neuro-secretion?), perhaps combined with abnormal vascular tissue sensitivity, under the influence of emotional, thermal, mechanical and inflammatory conditions. Peculiarities of sex distribution and age prevalence suggest gonadal influences. Sympathectomy and sympatholytic drugs prove often, though not regularly, effective in the treatment of these disorders.

The underlying mechanism of rare conditions, associated with abnormal local arterial dilatation, redness, heat and pain is unknown and no effective methods have yet been devised for their treatment.

Periarteritis Nodosa

Definition and General Principles

Since its original description by Kussmaul and Meier in 1866¹⁹⁶³, the syndrome of periarteritis nodosa has baffled diagnosticians and pathologists alike because of its whimsical symptomatology and enigmatic pathogenesis.

Its morphological substrate consists of irregularly distributed necrotic foci which develop at the medio-adventitial junction of the smaller and medium-sized muscular arteries. In these foci, an initial accumulation of leukocytes, largely of the eosinophil type, is followed by the formation of granulation tissue in a nodular arrangement of not more than a few millimeters in diameter. Intimal proliferation occurs in the vicinity of the nodules, local thromboses, arterial ruptures or, in the quiescent chronic phases, obliterating scar formations, may lead to serious damage of the affected tissue areas and organs.

Due to the wide variations in the speed and extensiveness of development of the vascular lesions and to their entirely unpredictable distribution over the arterial system, the clinical manifestations are extremely variegated. They are often confused with other diseases, especially with those which seem to share certain elements of their pathogenesis with periarteritis nodosa, such as rheumatic fever, glomerulonephritis, polyneuritis and others. On superficial examination, periarteritis nodosa can be easily mistaken for typhoid fever, miliary tuberculosis, subacute bacterial endocarditis, cholecystitis, appendicitis, peritonitis, Hodgkin's disease, Schonlein-Henoch purpura, polymyositis, trichinosis, etc. The renal involvement may be accompanied by more or less rapidly developing hypertension and end up in uremia. Periarteritis nodosa of the coronary vessels may provoke electrocardiographic signs of myocardial damage, effusive pericarditis and fatal congestive failure.

Since recognition of the not quite so rare occurrence of periarteritis nodosa has become more widespread, the diagnosis is being made with increasing frequency. A history of preceding allergic manifestations and signs, suggestive of an allergic disposition, serve as generally useful, though sometimes deceptive, diagnostic criteria. Some of these are the following: bronchial asthma, eosinophilia, unexplained febrile temperatures, rapid sedimentation rate, slight anemia, muscular pains, abdominal complaints without evidence of gross pathology, nephritic signs with hypertension and

retinitis. The biopsy of palpable subcutaneous nodules on the extension surfaces and elsewhere is apt to establish the diagnosis with certainty.

Men, mostly of the middle-age groups, are somewhat more often affected than women.

The prognosis depends on the degree of involvement of vital organs, thromboses, hemorrhages and other complications. Spontaneous recoveries, though uncommon, seem to occur in some instances. Newer methods of hormone treatment may significantly improve the outlook for survival and recovery (see below).

Hormonal Aspects of Pathogenesis

Connections between the pathogenesis of periarteritis nodosa and the endocrine system have been suspected for a long time, as was only natural concerning a disease with obscure origin. Older speculative considerations¹²³ have been superseded more recently by a systematic concentration on the pituita-adrenocortical axis. Selye's experimental observations have shown that vascular lesions very much like those of clinical periarteritis nodosa can be elicited in animals with considerable regularity by the application of mineralocorticoids and extracts from the anterior lobe of the pituitary³⁰⁷⁷. Similarities of the experimentally induced vascular lesions and of their distribution, with those seen in clinical cases, were noticed also by other workers (ht., see³⁰). Selye considers the manifestations of periarteritis nodosa as representing a classical example of the "diseases of adaptation"

Production of mineralocorticoids. A pathogenic identity of the desoxycorticosterone-induced lesions and those of clinical periarteritis nodosa is being postulated on these grounds. Selye admits however that it may not be the excess mineralocorticoids per se which cause the vascular changes but their cooperation with some pre-existing hypothetical "stressors" or "isotoxic factors."

Glucocorticoids were found to counteract the periarteritis-inducing effects of mineralocorticoids to some extent with the exception of those in the heart³⁰⁷⁷. Pituitary extracts which stimulate prevalently the elaboration of glucocorticoids, are said to cause marked periarteritis only in the heart and not in other organs³⁰⁷⁷.

Hormonal Aspects of Treatment

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apeutically effective in cases of clinical periarteritis nodosa, despite its presumable pituitary-adrenocortical origin.

Impressive, even though only limited and temporary, results were achieved in several instances with 40–150 mg of ACTH per day^{472, 1135, 2858, 3115, 3257} or with cortisone in total doses of 3.6 to 13.4 grams, administered over 11 to 21 weeks respectively³¹¹⁸. Disappearance of fever, normalization of the sedimentation rate and blood pressure, and general symptomatic improvement could be maintained for varying periods of time; but in some of the cases death occurred despite resumption of treatment and despite the fact that healing of fresh arterial lesions could be bioptically⁴⁷⁸ and autoptically³¹¹⁸ ascertained. It seems that the healing process of the vessels is accompanied by secondary fibrous obliterations and results in injurious effects upon the tissues involved.

Summary

Histological analogies between the clinical syndrome of periarteritis nodosa and similar lesions, experimentally produced by the administration of anterior pituitary extracts and DCA, suggest that periarteritis nodosa may be classified as one of the "diseases of adaptation" to various stressful conditions, largely of an infectious and allergic nature. Striking, although limited, therapeutic results were achieved in this heretofore intractable disease by the administration of ACTH and cortisone.

Angina Pectoris

Definition and Symptomatology

The term "angina pectoris", introduced in 1768 by Heberden, will be used in the following discussion to denote those types of uncomfortable or painful sensations of varying location and intensity which can be assumed to originate in the heart muscle as the result of an acute state of local hypoxia, i.e., of a discrepancy between the amount of oxygen consumed by the myocardium and the amount of oxygen supplied to it per time unit. It should be understood that according to this definition angina pectoris is not to be regarded as one single, sharply circumscribed morbid entity, but rather as the corollary of coinciding circumstances which share one common phenomenon, namely painful acute myocardial hypoxia. The pain which is occasioned by prolonged myocardial anoxia, as in the case of coronary occlusion, is also referred to as angina pectoris by some workers but will not be included in this section.

The anginal syndrome occurs by far more frequently in males than in females, the sex ratio being estimated as between three and six to one¹²⁵.¹²⁶ Most women with angina pectoris are at the same time hypertensive¹²⁷.¹²⁸ while in male angina patients this combination is less common¹²⁹. Although more than 90 per cent of the cases were reported to develop beyond the 40th, and more than 70 per cent beyond the 50th year¹³⁰, relatively large numbers of instances of angina pectoris in young soldiers were

... special treatises devoted to this subject¹³¹.
¹³² It may suffice, therefore, to mention as salient points: (a) the variability of the location of pain, feeling of oppression or numbness (retrosternal area, throat, jaw, upper extremities, especially the left shoulder, arm, wrist, hand, epigastrium, rarely precordium near the apex, left upper chest, interscapular and circumoral region), (b) the short duration of the attacks which ranges between one or two minutes and a half

... is tachycardia nor an abnormal elevation of the blood pressure. Anxiety is not commonly experienced in

angina pectoris as defined above, in contrast to its prevalence in connection with *coronary occlusion*.

There are close topical relationships between the afferent, pain-conveying sympathetic fibers of the heart and the spinal nerves, especially of the segments D1-D5^{650, 2336, 3590}. This accounts for the fact that the above-mentioned irradiations of pain into shoulder and arm are sometimes markedly aggravated by factors which affect the *somatic nerves primarily*^{313, 1506}, such as osteoarthritis and other deformities of the thoracic spine^{1201, 2609, 3169}, *myalgias, cervical ribs and the like*. Conversely, anginal symptoms may be mimicked by conditions of the latter kind^{652, 2609, 3459}. Neural connections in the cervical area³⁵¹¹ and in the innervation of the anterior chest wall^{3420, 3511} may add further to diagnostic confusions¹⁷⁰.

Precipitating Factors

Because of the lack of objectively discernible physical signs, the diagnosis of angina pectoris has to be largely based on the case history, whereby particular significance must be attached to the conditions which, according to the patient's experience, are most likely to provoke the familiar symptoms. The most common occasion for anginal pain is *muscular exercise* such as walking fast, climbing uphill, lifting heavy objects, etc. ("angina on effort"). It is worthy of note, however, that the quantitative aspects of physical work appear often less decisive than its association with certain features of a psychological nature. The writer knew a patient who experienced anginal symptoms almost exclusively when having to drive his car in reverse, while he was able to walk fast, or to practice light gymnastics without trouble, others had no difficulty climbing stairs in their own homes or promenading extensively without any definite goal, while it was impossible for them to walk only a fraction of those distances with the explicit intention to reach a certain place at a certain time for a certain purpose, no matter at how slow a pace. If special attention is paid to the frame of mind in which physical exertions are undertaken by patients with angina pectoris, it will not infrequently be found that pain occurs only or prevalently under the aggravating influence of mental tension or mere awareness of purpose and that much heavier muscular work, devoid of such connotations, can be performed with relative ease. To sensitive and fearful individuals who had suffered attacks of pain on walking, and who, in addition, had read or had been told by their physicians about the connections between exercise and angina, every physical effort will become a mental problem and source of anxiety, thus perpetuating the pain-evoking linkage of psychic anticipation and even minimal muscular work.

The occurrence of anginal symptoms under purely *emotional circumstances* is well known⁴⁰. Here again there is no clear-cut relationship between

the "quantitative" intensity of an emotional situation, such as anger, fear, disappointment, etc., and the readiness with which anginal symptoms will occur. One of the writer's patients who used to develop pain on the slightest physical or mental provocation spent 20 minutes flying in a burning airplane, helping to put out the flames, and without experiencing any anginal symptoms either during or after the ordeal. It is said that intense sudden fright induces vagal stimulation, as indicated by slowing of the heart rate, and it appears conceivable that this mechanism may help to overcome the usual sympathetic reaction which prevails with other emotional stimuli. Anger and similar acute mental attitudes, resulting from thwarted intentions, unwelcome criticisms, and the like, even from quite trifling incidents which go against the patient's "grain", are most likely to set those neurovegetative forces into motion which elicit anginal attacks. An increase of cardiac output and accelerated circulation was observed by several investigators during emotional stress^{1292 1301 1310 1313 1360 1361a 1362}. These cardiovascular changes resembled the reactions produced by small doses of epinephrine^{1301 1321a}. Electrocardiographic tracings, obtained from patients in an acute state of fear, showed also characteristics reminiscent of the effects of epinephrine^{1302 1307a 1321}.

Other common angina-provoking conditions are exposure of the face to cold wind¹²²⁷ (more so than, e.g., of the entire body to a cool shower bath), exercise performed in a cold environment¹²¹³, with cooled hands¹⁰¹⁰ or after food intake¹³¹⁷, the digestion of a heavy meal, straining at stool, and sexual intercourse.

Intense tobacco smoking^{1213 1232 1245}, the administration of epinephrine^{1229 1210 1247 1259 1260}, and artificially induced or spontaneous insulin hypoglycemia (p. 221) are likewise capable of precipitating anginal pain.

Electrocardiographic manifestations (depression of S-T and flattening, diphasicity or inversion of a previously positive T in leads I, II and in some of the precordial leads) are often provoked in angina patients by physical exercise, as first observed by Wood and Wolferth¹²⁷³. This reaction was introduced as a diagnostic test by Goldhammer and Scherf^{1234 1266} and later standardized by American workers (Master¹²¹⁶ and others^{1216 1272a}). The occurrence of anginal pain and electrocardiographic changes during inhalation of low oxygen concentrations was described by Dietrich and Schwegel¹²¹⁰. It was also utilized for diagnostic purposes by American clinicians (Levy¹²⁰² and others^{1228 1241}), with occasional untoward side effects^{1216 1233}. The epinephrine test¹²¹⁰ is even more dangerous¹²²⁹ and the diagnostic injection of pitressin^{1228 1240} proved equally hazardous¹²¹⁰, but, as a rule, none of these tests is necessary to arrive at a correct diagnosis, nor can any one of them be considered as absolutely reliable.

Attacks which make their appearance not only under the above-enumer-

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The occurrence of anginal symptoms under purely emotional circumstances is well known⁴⁰. Here again there is no clear-cut relationship between

tion of epinephrine^{1,60} was witnessed by the writer first hand when, at the age of 32, he injected into himself for the purpose of some blood fat studies, 13 mg of that powerful hormone. Incidentally, this unforgettably terrifying experience initiated his interest in the role of sympathomimetic catecholamines in the pathogenesis of anginal pain and of other forms of cardiovascular pathology.

The finding of histological abnormalities in the thoracic sympathetic ganglia of patients with angina pectoris²⁰⁹ does not seem to have been confirmed by other workers.

General Pathogenic Considerations

Present-day views of the pathogenesis of angina pectoris are practically without exception focused on the central feature of acute myocardial hypoxia, the importance of which was convincingly emphasized by Keefer and Resnik in 1928¹⁷²⁹, and later experimentally confirmed by Dietrich and Schwiegl⁷²³ and others²⁴⁰⁰⁻²⁴⁰¹.

It is obvious that coronary sclerosis alone, being a static condition, cannot possibly account for the acute episodes of myocardial oxygen deficiency which are generally assumed to cause the typical anginal sensations. Besides, it has been shown that the degree of coronary narrowing which must be reached to diminish the coronary circulation significantly⁷²⁰² is greater than that detectable at autopsy in many cases of angina pectoris.

1. Maintenance of coronary flow²⁴²².

To explain the acuteness of pain-producing myocardial hypoxia, it is therefore necessary to postulate rapidly arising and subsiding conditions which would create a temporary quantitative discrepancy between the amount of oxygen consumed by the heart muscle, and the amount simultaneously offered by the coronary arterial blood. Such can be—

(a) A permanent decrease in coronary flow (either because the sclerotic coronaries are not capable of normal compensatory dilatation or because cardiac work has risen to such an extent that even normal coronary vessels cannot dilate sufficiently to fulfill the excessively increased oxygen requirement),

(b) A temporary decrease of coronary flow due to spastic constriction of the coronary arteries,

(c) A temporary decrease of coronary flow due to a fall of systemic blood pressure,

(d) A temporary decrease of coronary flow due to peculiar hemodynamic

ated voluntarily induced and, to some extent, avoidable conditions, but which arise at physical and mental rest and during sleep without any definite provocation, are designated as "angina decubitus". If occurring in patients who had suffered for some time from angina on effort, emotion, etc., or who had survived a myocardial infarction, they have to be considered as an ominous development, foreboding more serious complications and possibly sudden death in the not too distant future.

A less fateful prognostic significance is to be attached to anginal pains which are felt in connection with attacks of *paroxysmal tachycardia*²⁹⁴, by patients with *mitral stenosis*²⁹⁷, *aortic valvular lesions*³⁰⁰ and during *hypertensive crises*, caused by *pheochromocytomas* (p. 85) or other "sympathetic storms".

The incidence of angina pectoris in thyrotoxic and myxedematous individuals has been discussed on pp. 136 and 152.

Pathology

The post-mortem finding of sclerosis of the coronary arteries of a major or minor degree in cases of angina pectoris is encountered with such regularity^{274, 1882, 2268} that a causal relationship appears established beyond doubt, even though there are numerous instances of coronary sclerosis without a history of anginal symptoms on record^{1841, 2272, 2641}. On the other hand, absence of anatomical lesions of the coronary vessels does not necessarily preclude the occurrence of the anginal syndrome. It is possible, however, that in some cases in which the coronary arteries were found intact^{29, 1841, 1943, 2421}, the clinical diagnosis may have been incorrect or that morphological exploration may have been inadequate¹⁶⁰⁹, particularly concerning the detection of occlusions of smaller coronary branches^{308, 310, 1572, 2038}. The results of statistical studies concerning the incidence of such occlusions in relation to that of anginal symptoms are strongly suggestive of their pathogenic significance³¹⁰. In some cases with apparently normally patent coronary arteries, a partial occlusion of the coronary ostium, due to syphilitic aortitis, may have been overlooked¹⁰⁶⁰. Nevertheless, it must be kept in mind that a narrowing of the coronary bed, either "organic" or "spastic", is not a necessary prerequisite for the occurrence of anginal symptoms and of their electrocardiographic equivalents.

There are certain valvular lesions which are believed to interfere with an adequate blood supply to the myocardium and thus to contribute to the appearance of anginal manifestations (see above). Furthermore, it is known, as mentioned in the preceding section, that in otherwise normal hearts, anginal symptoms can arise under the influence of excessive adrenergic stimulation. The possibility to provoke extremely severe anginal pain and an "anoxic" electrocardiogram in young healthy individuals by administra-

existence of reflex mechanisms, involved in the production of pain. It appears at least doubtful that such local cold stimuli should have caused an augmentation of cardiac work to higher degrees than they are likely to occur in the same patient at other times without evoking symptoms. Besides, it has been stated that an augmentation of cardiac work per se, apart from nerve-induced alterations of the myocardial metabolism, exerts only little effect upon the oxygen consumption by the heart^{122a}.

A systematic study of the behavior of blood pressure and heart rate before and at half-minute intervals during and following exercise, accompanied by anginal symptoms^{121b}, revealed both elevations and decreases of

TABLE 17
Examples of Discrepancy Between Cardiac Work and the Occurrence of Anginal Pain
(After W. Raab^{121b})

CASE		BLOOD PRESSURE	HEART RATE	ANGINAL PAIN
1	Rest	120/65	64	—
	Rest	150/70	70	—
	Spontaneous attack	150/80	64	++
	Spontaneous attack	120/70	85	+++
	Exercise	160/90	90	—
2	Rest	160/75	96	—
	Spontaneous attack	160/80	100	+++
	Exercise	195/90	104	—
3	Rest	140/75	65	—
	Spontaneous attack	150/75	88	+++
	Exercise	155/70	100	—

the blood pressure. Although the pulse frequency proved constantly elevated during exercise, the conclusion was reached that "the wide variation in systolic blood pressure and heart rate at the onset of attacks of angina indicates that such changes are not primarily etiological factors in their precipitation"^{121b}. This statement corroborates earlier observations of the writer²⁶⁵ which showed that frequently no relationship whatsoever can be detected between the occurrence of anginal attacks and the degree of cardiac work, as estimated from the blood pressure fluctuations and heart rate. During anginal attacks, occurring spontaneously at rest (angina decubitus), both blood pressure and heart rate were found in several instances to be equal to or lower than those measured at other times in the same patient when free of symptoms (Table 17). Furthermore, a follow-up of a series of patients in whom the anginal symptoms had completely or almost

and anatomical conditions affecting the coronary circulation (valvular lesions, etc.);

(e) A temporarily insufficient oxygen supply to the heart muscle during increased cardiac work because of anemia of a degree which would make the coronary flow inadequate;

(f) A temporary increase of the oxygen consumption by the heart muscle beyond the requirements of cardiac work, for the compensation of which the blood supply, offered by either sclerotic or even dilated coronary vessels, would not suffice;

(g) Any combination of these alternatives.

Ad (a): As discussed on p 364, physical exercise is one of the most important precipitating factors of angina pectoris. Its association, as well as that of certain emotional states, with an augmentation of cardiac muscular work is well enough known not to need any special emphasis. In fact, the notion that (barring anemia and other unusual interferences) increased cardiac work constitutes the one and only condition which (in the presence of coronary sclerosis) is capable of eliciting temporary angina-producing myocardial hypoxia, is firmly entrenched in the minds of most clinicians. It seems advisable, however, to take a closer look at this allegedly inseparable causal linkage between anginal pain and an increase of cardiac work, the degree of which alone is supposed to determine the appearance or non-appearance of anginal symptoms. Does there really exist any conclusive evidence which would indicate that cardiac pain cannot arise in the coronary sclerotic patient except while the heart muscle is performing a greater amount of work than it does in the same patient at any time during which he is free from pain? Only few studies have been devoted to this crucial question by comparing the hemodynamic situation during anginal attacks with that existing in the interval. As was to be expected, some such observations revealed a rise of blood pressure and heart rate or of both during anginal pains^{235, 2015, 2291, 2221, 2560}, especially in connection with hypertensive crises^{2981, 3125}. On the other hand, it has been emphasized by Altschule³⁷ that "it is not valid...to conclude that attacks of angina pectoris are in every instance associated with increased cardiac output," and "...angina may occur when the work of the heart is not increased...or even when cardiac work is actually decreased." Observations of this latter kind have been made in psychic situations of desperation and defeat which were accompanied by cardiac pain in the face of a diminished cardiac output²⁶⁸⁰.

The fact that local application of ice to one hand during exercise reduces the exercise tolerance of patients with angina pectoris and results in the precipitation of pain in a warm room³⁰⁴² was interpreted as indicating the

changes in the work load of the heart, myocardial ischemia may develop if the efficiency decreases as the result of "chemical processes." However, here, too, no reference is made to the chemical action of the ever-present sympathomimetic neurohormones, the eminent importance of which in the origin of myocardial hypoxia will be discussed on p 373 ff.

Ad (b) The hypothesis of a *coronary arterial spasm* as the cause of anginal pains^{1027 1028 1029 1030} owes its existence and still wide-spread popularity to the desire to find an explanation for the apparent discrepancy between a history of anginal symptoms during lifetime and absence of anatomical changes of the coronary arteries, which is found post-mortem in some instances. The spasm hypothesis was construed, moreover, in order to reconcile this discrepancy with the allegedly all-important requirement of diminished coronary flow for the origin of angina, and to interpret various other phenomena in terms of a postulated coronary constriction. For instance, the phenomenon of precipitation of anginal symptoms by cooling one hand was ascribed to a presumable reflectory constriction of the coronary vessels¹⁰⁴², and there are countless other examples of similar conclusions which appear more or less necessary, indeed, as long as the crucial phenomenon of neurohormonal catecholamine-induced myocardial hypoxia in the presence even of an optimal coronary flow and in the absence of increased cardiac work (p 374 ff) is not taken into consideration.

It is true that for a long time the coronary constriction hypothesis served its purpose to bridge an imaginary gap and that it benefited from the circumstance that its correctness is as difficult to disprove as it is to prove. However, the fact remains that a "coronary spasm" has never been clinically demonstrated. The only agent which is known to produce coronary spasms is pitressin (p 43). Furthermore, anginal attacks occur typically under conditions which are associated with sympathetic stimulation and discharges of epinephrine, and that both of these dilate rather than constrict the coronary vessels.

Perhaps the most suggestive argument in favor of a coronary constrictive element in the mechanism of angina pectoris is the instantaneous therapeutic efficiency of nitroglycerine and other nitrates, the coronary dilator action of which has been extensively established¹⁰³⁸. However, here again another alternative is being generally disregarded, namely a possible direct action of the nitrates upon the heart muscle. Certain indications for an antagonistic effect of nitroglycerine against those metabolic alterations of the myocardium, which seem to produce anginal pain¹⁰³⁹, will be discussed on p. 405 ff. The abolition of the electrocardiographic signs, connected with the anginal attack, by the intake of nitroglycerine¹⁰⁴⁰ does not need to be interpreted exclusively in terms of coronary dilatation and conversely the therapeutic

completely disappeared for periods of several months following roentgen irradiation of the adrenal glands²⁶⁶², did not disclose any regularly depressing effect of this type of therapy on the blood pressure level and cardiac activity. On the contrary, in some instances the blood pressure showed a rising tendency, while the anginal symptoms disappeared. These latter findings confirm in reversed direction the long-known fact that the progression of angina pectoris in a given case does not display any regular proportionality to the behavior of blood pressure and heart rate. It is also a matter of common knowledge that many patients with angina pectoris suffer intensely at the outset of a walk or other intentional exercise but are capable of considerably greater physical effort, once the initial symptoms have worn off, or that the same patient who is unable to walk one block

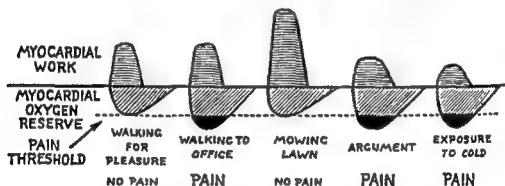


FIG 48 Hypothetical graph, designed to explain incongruities of the degree of cardiac work and of the occurrence or non-occurrence of anginal pain under various conditions. Some of the (e.g. psychogenic) of hypoxia (exhaustion) ■

without discomfort can chop wood or engage in calisthenics and not notice any pain (Fig 48)

The above-raised objections against the almost universal over-estimation of the factor of cardiac work in the origin of anginal symptoms, have been dwelt on in some detail in order to prepare the readers' receptiveness for the consideration of other existing alternatives which will be discussed on p. 373 ff.

The imperturbability with which most clinical articles and textbooks insist on the primacy of increased cardiac work in the pathogenesis of angina pectoris, as on an infallible religious creed, is not surprising, since it is paralleled by an equally persistent disregard of some of the fundamental physiological facts of cardiac metabolism and of its neurohormonal regulation which is largely independent of the degree of myocardial work and of coronary flow. As a rare exception, an article by H. Hecht on "Concepts of myocardial ischemia"¹⁴²³ contains the statement: "Without apparent

Ad (f): An excessive, hypoxia-producing oxygen consumption by the heart muscle as a primary biochemical phenomenon, relatively independent of the magnitude of cardiac work, and potentially painful, is mentioned here not as a purely speculative theoretical conception but as an established reality which has been recognized and studied by physiologists and pharmacologists for the past 34 years. In the writer's opinion, it constitutes a factor of paramount importance in the pathogenic mechanism of most cases of angina pectoris, even though it is being steadfastly disregarded by clinical workers and pathologists alike with only a few exceptions. Since the phenomenon in question is induced by neurohormonal and hormonal action, it will be discussed in the following special sections

Role of Adrenal and Sympathogenic Neurohormones

Before entering into a discussion of the probable role of nor-epinephrine, secreted by the cardiac sympathetic nerves into the myocardial effector cells and of adrenal medullary epinephrine and nor-epinephrine reaching the heart muscle via the blood stream, in the pathogenesis of angina pectoris, it will be necessary to recapitulate briefly some of the basic facts concerning the intervention of the adrenosympathogenic catecholamines in myocardial metabolism

Epinephrine possesses the qualities of an oxidation catalyst and exerts a stimulating effect on general oxygen utilization¹²³. In particular it is known to exert a powerfully augmenting influence upon myocardial oxygen consumption (p. 11 ff). This peculiarity it shares with its demethylated homologue, nor-epinephrine, even though the calorigenic effect of the latter is considerably less intense than that of epinephrine¹²⁴. It is readily to be understood, therefore, that stimulation of the cardiac sympathetic nerves, which acts upon the heart by means of a neurosecretory discharge of nor-epinephrine (and possibly some epinephrine) into the myocardial cells, results in a marked increase of cardiac oxygen consumption

If these increments of myocardial oxidative activity would occur in direct proportion to the increase of cardiac dynamic performance, elicited by adrenosympathogenic interference, the traditional allegation that myocardial hypoxia during exercise, emotions, etc., is ascribable essentially to the exaggeration of myocardial work would be justified. This, however, is not the case in view of an important phenomenon which was discovered by Evans in 1917¹²⁵. He arrived at the conclusion that "the effect of adrenalin (on oxygen consumption by the heart) cannot be traced to purely mechanical factors, the increased metabolism is apparently due to a direct and specific effect in increasing and accelerating the chemical changes associated with contraction." Gollwitzer-Meier and her co-workers (1936)¹²⁶ stated that epinephrine increases myocardial oxygen consumption not only far

action of the nitrites represents no valid proof of a coronary constriction in angina pectoris²⁷⁰⁹.

Ad (c): Observations concerning the presence of myocardial necroses in the hearts of patients who had undergone severe shock¹⁰⁶¹, suggest the possibility that anginal symptoms which are occasionally observed following a precipitous fall of the systemic blood pressure may be caused, at least in part, by an insufficient blood supply to the myocardium²²⁵².

Ad (d): *Unusual hemodynamic and cardiac anatomical conditions*, existing in cases of valvular lesions, such as aortic stenosis and mitral stenosis, have been made responsible for the occasional occurrence of severe anginal pains in patients afflicted with these diseases but presenting normal coronary vessels at autopsy^{1061, 1063, 1959}. A critical discussion of the theories which have been advanced for the explanation of such events can be omitted here as not falling within the scope of this review. The possibility of a participation of acute neurohormonal metabolic effects upon the heart muscle has not been considered by the respective investigators.

Intense anginal attacks, occurring in young patients with rheumatic aortic insufficiency, mostly at night^{895, 1967, 2012, 2057} and associated with hypertensive paroxysms^{1060, 2297}, were ascribed to the low diastolic pressure level characteristic of aortic insufficiency¹⁶⁰³, and to a low coronary flow supposedly resulting from it. On the other hand, the usual rise of the diastolic pressure during the attacks²⁹⁵⁷, the finding of an increased coronary flow, obtained in patients with aortic insufficiency by means of coronary sinus catheterization²⁶⁴, and the partial normalization of depressed S-T segments and T waves in such patients immediately after exercise²²⁶, cast some doubt on the validity of the above-mentioned interpretation, at least as far as the origin of pain during the hypertensive episodes is concerned. Again, the possibility that neurohormonal hypoxiating influences might give rise to the painful attacks has not been considered.

Ad (e): Although the occurrence of angina pectoris in patients with anemia was reported in a considerable number of instances^{351, 1604, 2600, 2642}, and although it seems conceivable that the low oxygen content of the anemic blood might serve as the cause of anginal symptoms during exercise, etc., it has been stated that in almost all autopsied cases which had presented both anemia and angina pectoris, severe coronary sclerosis or syphilitic stenosis of the coronary ostium was found to exist^{1472, 2707}. This makes it probable that anemia acts occasionally as a contributory factor in the origin of the anginal syndrome but hardly ever as the primary cause per se¹⁰⁶⁰.

50) Endorsing the designation of epinephrine as an "anoxiating agent"¹¹¹, the authors arrive at the conclusion that "even after cardiac work is markedly reduced, nerve stimulation elevates cardiac oxygen consumption

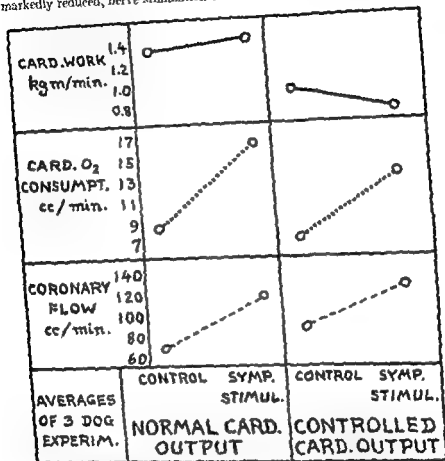


FIG. 50 Stimulation of the cardiac sympathetic nerves augments myocardial oxygen consumption regardless of simultaneous increase or decrease of cardiac work, as a specific chemical effect of local nerves . . . upon myo-

bel, C. V.

and coronary blood flow. Sympathetic nerve stimulation, by releasing an adrenalin-like substance, renders the heart anoxic and inefficient. The interpretation of coronary vasomotor changes requires knowledge of the myocardial metabolic requirements." This last sentence contains in a nutshell the most important and least heeded principle of neurogenic cardiovascular pathology. The "adrenalin-like" substance in question was in the meantime

beyond the compensatory effectiveness of the simultaneously increased coronary flow, but also far beyond the oxidative energetic requirements of the more vigorously and faster beating heart, and for a considerably longer period of time than the increase of cardiac work persists¹¹⁹⁹. In other words, epinephrine causes an uneconomical, wasteful consumption of oxygen by the heart muscle which occurs more or less independently of cardiac work. It leads to marked cardiac hypoxia, unless counteracted by the metabolically opposite effect of cholinergic vagal activity which depresses myocardial oxygen consumption and renders it more economical^{1199a, 2735}.

The same principles were demonstrated by Gollwitzer-Meier and Kroetz

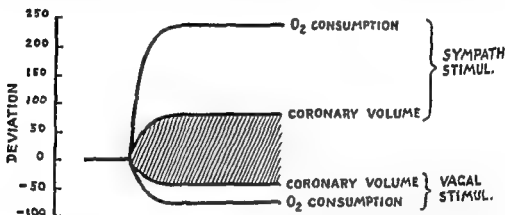


FIG 49 Stimulation of the cardiac sympathetic nerves increases myocardial oxygen consumption to a greater extent than coronary flow, thus producing myo-

^{1199a} for the neurogenic discharge of sympathomimetic catecholamines (mainly nor-epinephrine) in the myocardium. Electrical stimulation of the cardiac nerves (Fig. 49) was accompanied by a disproportionate increase of myocardial oxygen consumption and coronary flow during sympathetic stimulation on one hand, and by a disproportionate diminution of myocardial oxygen consumption and coronary flow during vagus stimulation on the other. Similar results were obtained by Shipley and Gregg¹¹²³, concerning sympathetic stimulation.

Further evidence for the myocardial oxygen wastage, occurring during electrical stimulation of the cardiac sympathetic nerves, was presented by Eckstein and co-workers¹²², who showed that this procedure was accompanied by an augmentation of coronary flow and, significantly, by a marked increase of myocardial oxygen consumption, even when cardiac work was artificially diminished by mechanical control of the cardiac output (Fig.

and that sympathetic denervation of the heart is followed by a diminution of the myocardial catecholamine deposits^{120a, 271d}.

In view of the above-enumerated facts, the phenomenon of adreno-sympathogenic, catecholamine-induced acute chemical hypoxia of the heart muscle appears as one of two conditions, the coincidence of which is necessary to initiate the common type of anginal symptoms. The other complementary condition consists of an impairment of adequate simultaneous

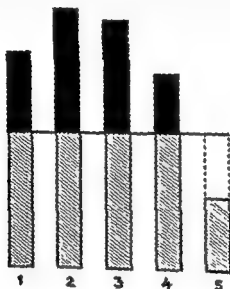


FIG. 51. Relative levels of conditions.

third element involved

...may be considered as a

Further arguments in favor of the concept of a ...

...discharged catecholamines in the heart muscle (Fig 51, also Fig. 55, ...

identified as consisting prevailingly of nor-epinephrine and only to a smaller percentage of epinephrine. The human heart contains an appreciably higher amount of epinephrine (compared with nor-epinephrine) than the hearts of other mammalian species^{1206a, 1561, 2698}.

Less clearly established than the fundamental fact of a chemically anoxiating action of the sympathomimetic catecholamines epinephrine and nor-epinephrine upon the heart muscle, is the nature of the underlying chemical processes. It seems worthy of note, however, that the metabolic changes, elicited in the heart muscle by epinephrine, notably a diminution of creatine, glycogen, phosphagen and adenylypyrophosphoric acid^{300, 443, 700, 920, 3031, 3052, 3523}, are identical with those found in experimentally anoxiated hearts^{1409, 3051} and in hearts analyzed after strenuous exercise^{3050, 3052}.

The accumulation of lactic acid in the heart muscle under the influence of epinephrine^{1224, 3052, 3523} and the resulting acidification of the coronary venous blood²¹⁸⁷, have been interpreted as indicating a deficiency in the aerobic utilization of lactic acid and an abnormal prevalence of anaerobic mechanisms of myocardial energy production³⁰⁵², while much of the oxidative energy seems to be lost in the form of heat^{1578, 1933}. It is clear that any impairment of the normally concomitant dilatation of the coronary arteries during epinephrine or nor-epinephrine action will be apt to accentuate the discrepancy between myocardial oxygen consumption and coronary oxygen supply to an extreme, "catastrophic"³⁰⁵² degree. Moreover, it is believed that a decrease of coronary irrigation will also jeopardize the "washing away" of accumulated non-oxidized metabolites, especially lactic acid³⁰⁵². This latter factor has been suspected of contributing substantially to the development of painful sensations^{2337, 3052} in analogy to conditions arising in the ischemic striated muscle²⁰¹³, and in view of the experience that a deficiency of the extrinsic oxygen supply alone, as e.g. in anemia, does not usually suffice to evoke pain, even during exercise^{1523, 2346}, unless coronary sclerosis coexists^{1000, 1473, 2702}.

Recognition of the above-discussed principle of catecholamine-induced chemical hypoxia of the myocardium, must be regarded as an indispensable prerequisite for the understanding of the pathogenesis not only of angina pectoris but also of other forms of neurogenic heart disease, as will be seen in several of the following sections. *The heart muscle contains under all*

post-ganglionic sympathetic fibers^{2077, 2099, 2182}, epinephrine^{1206a, 1561, 2698} of adrenal origin and probably also epinephrine which is being liberated by intracardiac chromaffine islets¹⁵⁴¹. It was found by the writer and his associates that the heart muscle displays a greater tendency than other tissues to absorb and accumulate injected or secreted catecholamines (Fig 2, p 7),

with emphasis on coronary circulation¹⁰⁰⁰ and in the German post-war literature with emphasis on cardiac dynamics^{302, 303, 304}. In the writer's opinion, the decisive mechanism which exhausts and finally transgresses the margin of "coronary reserve" in the common forms of angina pectoris is essentially a chemical one, induced by direct interference of the oxygen-wasting adrenosympathogenic catecholamines in myocardial metabolism (Figs 52, 53, 54, 55, 56)

Instances of prolonged cardiac pain, occurring at rest or during sleep, and suggestive of myocardial infarction but devoid of its pathognomonic criteria (fever, leukocytosis, elevated sedimentation rate, electrocardiographic infarction pattern) and not presenting signs of infarction at autopsy, are not too infrequently observed. In keeping with the dominating mechanistic tradition, an attempt was made¹⁰⁴¹ to interpret these occurrences as being caused by a "prolonged but reversible myocardial ischemia" and "acute narrowing or occlusion in the coronary tree" which would mean a return to the concept of the mythical coronary spasm. Similar hypothetical explanatory speculations can be found in the current clinical literature wherever the difficulty arises to reconcile existing symptoms of myocardial hypoxia with the absence of indications for a reasonably proportionate increase of cardiac work. However, since it is no longer necessary and justifiable to think exclusively in terms of cardiac "plumbing" in the face of the amply established hypoxia-producing chemical effects of adrenergic neurosecretion, cardiac episodes, like the above-mentioned ones, can and must be evaluated also from this latter point of view.

The same reasoning applies to the interpretation of the electrocardiographic changes, which usually occur during spontaneous attacks^{277, 2818, 2819} or during those induced by exercise^{1764, 2216, 2416, 2418, 2421, 2894} or by hypoxemia^{24, 271, 436, 713, 1242, 1711, 1922, 2007, 2341, 2360, 2551, 2623}. These changes consist of a

... of epinephrine or of catecholamines extracted from the myocardium of animals or humans^{739, 1710, 1961, 1962, 2229, 2416, 2466} (Fig. 57) and can sometimes be normalized by antiadrenergic ergot drugs.^{27, 1574, 2449, 2794}

The fact that injected nor-epinephrine usually elevates rather than depresses the T-wave (p. 14) cannot be construed as an argument against the epinephrine-like hypoxia-producing action of this neurohormone for the following reasons: (1) the T-wave-elevating effect of injected circulating nor-epinephrine is apparently caused by secondary vagal reflex effects, induced via the peripheral pressure-receptors as a result of the simultaneous

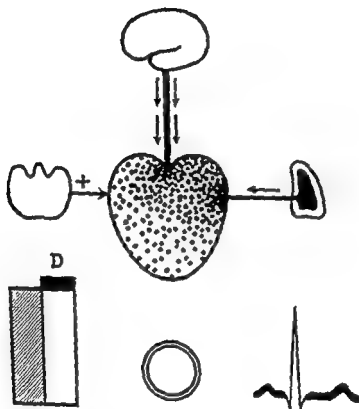
p. 383)²⁴⁴, namely: physical exertion, exposure to cold, emotional excitement, tobacco smoking, over-dosage of insulin; furthermore, after injection of epinephrine^{559, 1710, 1947, 3560} and during pheochromocytoma-induced paroxysms^{414, 1935, 2455}. Such attacks were found to be accompanied by an elevation of the blood epinephrine level³⁶⁹ and to disappear after operative removal of the tumor^{414, 1956}.

In all of 12 cases of angina pectoris, examined by the writer, the *acute increase of catecholamines in the blood after exercise* proved considerably higher than the average normal increase, while the resting levels were within normal range (Fig. 59, p. 393). This seems to indicate an exaggerated tendency of angina patients to discharge epinephrine (and some nor-epinephrine) from the adrenal medulla in connection with exercise, but larger series of observations would be necessary to evaluate the significance of this phenomenon statistically as a possibly general predisposing characteristic of patients with angina pectoris.

As far as the *neurovegetative and hemodynamic situation* in patients with the common type of uncomplicated angina pectoris during the symptom-free interval is concerned, there exist some divergencies of opinions which seem to be due in part to differences of the technical approach. Some investigators, using the ethyl iodide and acetylene methods, magnesium sulphate and a method based on pulse wave velocity respectively^{37, 182, 241, 2232}, did not find any significant abnormalities of cardiac output, volume and velocity of the circulation. On the other hand, a markedly diminished cardiac output in the majority of angina patients was concluded from cardioballistographic studies^{2234, 2234}. Qualitative abnormalities of the cardioballistogram were noted as a regular and possibly even diagnostic feature in individuals suffering from anginal symptoms²⁹⁵. Schimert^{202, 2003, 2004}, employing the Broemser and Ranke method, observed in 31 out of 37 cases of angina pectoris an increase of cardiac output, varying between 20 and 100 per cent (average plus 80 per cent), and an augmented pulse pressure, usually combined with a decreased peripheral resistance. These findings were interpreted as indicating an increased adrenergic sympathetic tonicity, especially in the earlier stages of angina pectoris. They would seem to be well compatible with the writer's above-mentioned observations concerning an apparently abnormal adrenosecretory excitability in such individuals and with the finding of an above average cardiac acceleration during exercise in angina patients²⁶⁹⁴.

The term "*coronary reserve*" denotes the margin of safety within which acute diminutions of coronary flow or increases of myocardial oxygen consumption or both combined can take place before producing that critical degree of myocardial hypoxia which will cause anginal pain. According to prevalent points of view, the term is being used in the American literature

NORMAL

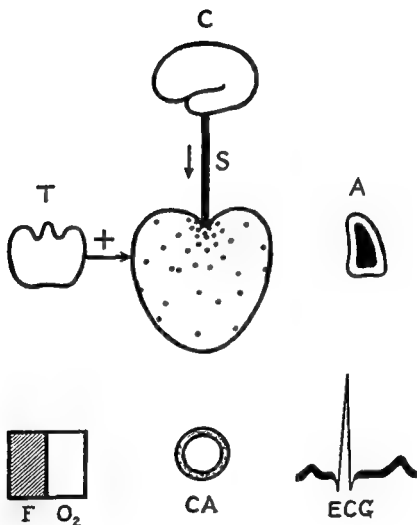


EXERCISE

FIG 53 During exercise the inflow of oxygenated blood is normal

(Adapted from Kohn, Rev argent. de cardiol 17: 1, 1950)

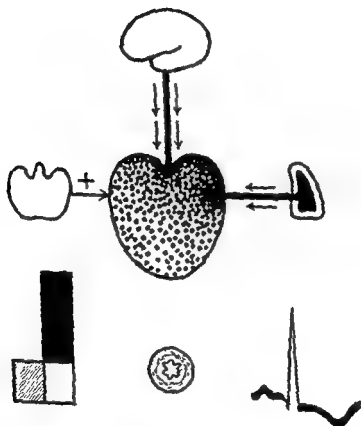
NORMAL



REST

FIG 52 This and the following figures depict the neurohormonal-hormonal pathogenic mechanism of angina pectoris and its rational treatment A adrenal gland (functionally no medullary secretion at rest), C brain, governing the sympathetic

CORONARY SCLEROSIS



EXERCISE WITH PAIN

Fig. 55. Diagram.

elevation of the diastolic pressure, for it disappears after atropinization¹⁴⁴, and in fully atropinized animals there exists no difference between the S-T- and T-wave depressing effects of epinephrine and nor-epinephrine^{145, 146}. (Figs. 3, 6, p. 14); (2) the extra amounts of nor-epinephrine, which are assumed to be instrumental in precipitating the pain-producing myocardial hypoxia in angina pectoris, do not circulate with the blood like the injected doses but are directly discharged into the myocardial cells from their supplying sympathetic fibers, consequently, they do not evoke general vasoconstriction, elevation of the diastolic pressure and vagal counter-effects but limit their sympathomimetic and hypoxiating action primarily to the heart muscle.

It is not yet known which of the biochemical features, attending the process of catecholamine-induced or low-oxygen-inhalatory myocardial hy-

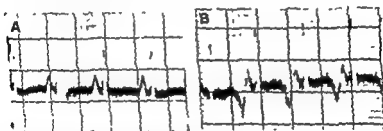
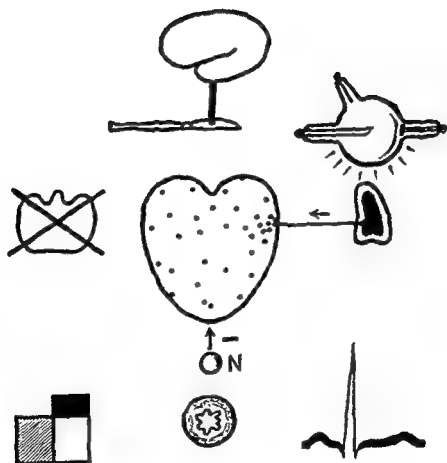


FIG. 57a, b. Catecholamines, extracted from the heart muscle, invert the T-wave in the atropinized cat. (The sensitivity of the electrocardiograph used for tracing B was slightly greater than that used in A.)

(After W. Raut, *Rev. argent. de cardiol.* 17, 1, 1933)

poxia, has to be held responsible for the characteristic electrocardiographic changes above mentioned. Whatever the finer mechanism may consist of, the writer cannot agree with the reasoning of those investigators who, unaware of the chemical effects of the catecholamines, feel compelled to adduce exclusively the concepts of coronary constriction or increased cardiac work in order to explain the neurogenic reflexory occurrence of "anginal" electrocardiographic signs and anginal symptoms, e.g., under the influence of local applications of ice^{227, 1042}, in connection with subdiaphragmatic biliary, gastric and intestinal episodes^{219, 1000, 1027, 2734}, and in cases of esophageal hiatus hernia^{230, 691, 1070, 1095, 2346, 2452}. Although a diminution of coronary blood flow has been actually elicited by distention of the stomach^{1069, 1277} and esophagus^{732, 733}, it should be kept in mind that a mere restriction of the coronary blood supply, unless extreme, is unlikely to cause a serious degree of myocardial hypoxia³²⁵, if not associated with an anoxic

CORONARY SCLEROSIS



EXERCISE WITHOUT PAIN

... and ... the useful myocardial oxygen ... (a) sym- ... into the heart ...

elevation of the diastolic pressure, for it disappears after atropinization¹⁹⁵⁹, and in fully atropinized animals there exists no difference between the S-T- and T-wave depressing effects of epinephrine and nor-epinephrine¹⁹⁶².¹⁹⁷⁰ (Figs 3, 6, p 14), (2) the extra amounts of nor-epinephrine, which are assumed to be instrumental in precipitating the pain-producing myocardial hypoxia in angina pectoris, do not circulate with the blood like the injected doses but are directly discharged into the myocardial cells from their supplying sympathetic fibers, consequently, they do not evoke general vasoconstriction, elevation of the diastolic pressure and vagal counter-effects but limit their sympathomimetic and hypoxiating action primarily to the heart muscle.

It is not yet known which of the biochemical features, attending the process of catecholamine-induced or low-oxygen-inhalatory myocardial hy-

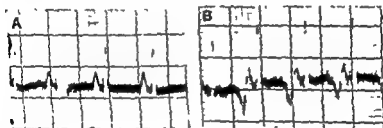


FIG 57a, b. ECG in the atropinized animal was slightly

reproduced from: *Argent de cardiol* 17 1, 1950)

poxia, has to be held responsible for the characteristic electrocardiographic changes above mentioned. Whatever the finer mechanism may consist of, the writer cannot agree with the reasoning of those investigators who, unaware of the chemical effects of the catecholamines, feel compelled to adduce exclusively the concepts of coronary constriction or increased cardiac work in order to explain the neurogenic reflexory occurrence of "anoxic" electrocardiographic signs and anginal symptoms, e.g., under the influence of local applications of $\text{Ac}^{227, 1957}$, in connection with subdiaphragmatic binary, gastric and intestinal episodes^{219, 1960, 1967, 2215}, and in cases of esophageal hiatus hernia^{220, 495, 1670, 1935, 2216, 2452}. Although a diminution of coronary blood flow has been actually elicited by distention of the

1969, 1977

etion of

serious

oxygen consumption by the heart muscle. According to Bayer²²⁰, inflation of the stomach is followed by quite different types of electrocardiographic

changes, depending on the either "vagotonic" or "sympathicotonic" constitution of the subject. Anginal symptoms occurred only in the latter group and the likelihood of a sympathogenic metabolic hypoxia as their causal mechanism is stressed by this author and by others^{2769, 3026}. Pain and marked electrocardiographic changes result from gastric inflation also in patients suffering from anginal attacks, arteriosclerosis and hypertension²⁷⁹³.

Similarly, the depression of S-T and T which appears in some individuals in the upright position was attributed by Nordenfelt²¹¹⁶ and others^{292, 2945} to an increase of the sympathetic tone rather than to a diminished coronary flow. There are many conditions (47 listed in one paper³⁰⁹⁴), not due to primary heart disease, in which electrocardiograms resembling those of angina patients, may be obtained. These conditions are of a very variegated nature, but it seems more than probable that neurohormonal metabolic factors are involved in the electrocardiographic manifestations of at least some of them. In the so-called "pulmo-coronary reflex", connected with pulmonary embolism^{1060, 2144, 2996}, the situation is probably complicated by other factors, such as the mechanical obstruction in the pulmonary vessels.

The writer is aware of the fact that due to his personal interest in the problems of adreno-sympathogenic neurohormonal interference in cardiac metabolism and in view of the much larger number of experimental observations concerning this particular aspect, he has not placed a great deal of explicit emphasis on the regulatory and *potentially normalizing* role of vagal cholinergic counteraction. A possible primary deficiency of the latter may

mutual cross-wise initiation of adrenergic and cholinergic activity within the effector cells⁶⁵³, the liberation of sympathomimetic catecholamines within the heart muscle under the influence of acetylcholine¹³⁶⁴, as demonstrated by Hoffmann and his co-workers¹³⁴⁴, the cardiac lesions produced by prolonged administration of acetylcholine¹³²⁷, probably via the last-named mechanism; and the observation of Wayne²⁵¹⁹ and Levine and Harvey¹⁹⁵⁹ that it is sometimes possible to stop anginal attacks by vagal stimulation, may serve as guideposts, pointing toward this largely unexplored area of knowledge which must be made accessible to our reasoning before a well rounded picture of the neurohormonal forms of metabolic cardiac pathology can be delineated.

The presence of histamine in autonomic nerves^{907, 909} and the functional balance between adrenergic and histamine-induced cardiovascular effects^{933, 3693}, may constitute an additional factor in cardiac metabolism. The

occurrence of appreciable amounts of histamine has been demonstrated also in the heart muscle itself¹⁴²².

Role of the Thyroid Hormone

Some aspects of the presumable significance of the thyroid hormone for the pathogenesis of angina pectoris have been discussed on p. 136 where reference was made to the occurrence of anginal symptoms in thyrotoxic individuals. It may suffice to re-emphasize here the fact that the dynamic and metabolic effects of epinephrine and of sympathetic stimulation (locally discharged catecholamines) upon the heart muscle are markedly intensified by the administration of thyroid hormone and weakened after thyroid inactivation (p. 35 ff., Figs. 52-56, pp. 380-384).

This principle is exemplified by the writer's observation²⁶⁷⁵ that thyroxine-treated rats tolerated only less than one-half of the normally tolerated maximal epinephrine concentration in the heart muscle (Fig. 10, p. 36) after injection of epinephrine, and the mortality was increased six-fold. Conversely, in thiouracil-treated rats, the tolerated myocardial epinephrine concentration was almost doubled and the mortality fell to one-sixth of that of untreated animals. Moreover, the writer found the electrocardiographic changes, induced by epinephrine injection in normal individuals, to be significantly weakened or abolished after treatment with thiouracil²⁶⁷⁹. The epinephrine-induced tachycardia (but not the blood pressure reaction) was likewise diminished after thiouracil. Similar observations, in which no place

is given to the absence of coronary lesions (stated at autopsy²⁶⁸⁴)

The most impressive proof of an important involvement of normal thyroid activity in the mechanism of angina is furnished by the therapeutic efficiency of thyroid inactivation [thyroidectomy, thiourea compounds, radioactive iodine (see following section)]. The credit for having systematically pursued this therapeutic approach from the surgical into the

chemical and pharmacological fields must be given to the *German School of Cardiology*. The writer must emphasize, however, as on previous occasions^{2679, 2680, 2682, 2683}, that he disagrees in part with the interpretation given by these workers to the underlying mechanism of the therapeutic effect of thyroid inactivation. He cannot follow their conclusion that the heart muscle requires a certain amount of oxygen and metabolites for its normal function. The heart muscle is a highly specialized tissue which can function without consideration

changes, depending on the either "vagotonic" or "sympathicotonic" constitution of the subject. Anginal symptoms occurred only in the latter group and the likelihood of a sympathogenic metabolic hypoxia as their causal mechanism is stressed by this author and by others^{2769, 2026}. Pain and marked electrocardiographic changes result from gastric inflation also in patients suffering from anginal attacks, arteriosclerosis and hypertension²²⁴⁷.

Similarly, the depression of S-T and T which appears in some individuals in the upright position was attributed by Nordenfelt²⁴⁴⁶ and others^{921, 2948} to an increase of the sympathetic tone rather than to a diminished coronary flow. There are many conditions (47 listed in one paper²⁰⁹⁴), not due to primary heart disease, in which electrocardiograms resembling those of angina patients, may be obtained. These conditions are of a very variegated nature, but it seems more than probable that neurohormonal metabolic factors are involved in the electrocardiographic manifestations of at least some of them. In the so-called "pulmo-coronary reflex", connected with pulmonary embolism^{1060, 2144, 2996}, the situation is probably complicated by other factors, such as the mechanical obstruction in the pulmonary vessels.

The writer is aware of the fact that due to his personal interest in the problems of adrenosympathogenic neurohormonal interference in cardiac metabolism and in view of the much larger number of experimental observations concerning this particular aspect, he has not placed a great deal of explicit emphasis on the regulatory and *potentially normalizing role of vagal cholinergic counteraction*. A possible primary deficiency of the latter may constitute an important factor in the mechanism of angina-producing neurogenic biochemical changes in the myocardium. This is a field in which much investigative work still remains to be done. Danielopolu's concept of a mutual cross-wise initiation of adrenergic and cholinergic activity within the effector cells⁶⁵⁹, the liberation of sympathomimetic catecholamines within the heart muscle under the influence of acetylcholine¹³⁶⁴, as demonstrated by Hoffmann and his co-workers²⁵⁴⁴, the cardiac lesions produced by prolonged administration of acetylcholine¹³³⁷, probably via the last-named mechanism; and the observation of Wayne²⁵¹⁸ and Levine and Harvey¹⁸⁹⁹ that it is sometimes possible to stop anginal attacks by vagal stimulation, may serve as guideposts, pointing toward this largely unexplored area of knowledge which must be made accessible to our reasoning before a well rounded picture of the neurohormonal forms of metabolic cardiac pathology can be delineated.

The presence of *histamine* in autonomic nerves^{907, 908} and the functional balance between adrenergic and histamine-induced cardiovascular effects^{933, 3693}, may constitute an additional factor in cardiac metabolism. The

A rational justification can be attributed to all those forms of treatment which are designed to *diminish sympathetic stimulation* and thus to reduce the influx of hypoxia-producing sympathogenic catecholamines (notably nor-epinephrine) into the heart muscle. The most primitive, yet a practically very important device, is that of physical rest and mental relaxation which should not be overdone, however, in order to avoid an exaggerated attitude of invalidism and boredom or frustration on the part of the patient. Situations which can be expected to elicit reflexory neurohormonal discharges into the heart, such as exposure to cold temperature, the ingestion of gas-forming food-stuffs or of heavy meals, and excessive tobacco smoking should likewise be avoided. As far as the latter is concerned, the complete abstinence from smoking is usually easier to maintain permanently than a partial restriction. Sedatives are useful in patients in whom a strong psychogenic element participates in the origin of the attacks (lit., see ¹⁰⁶⁰).

Paravertebral block of thoracic sympathetic ganglia with alcohol or procaine ^{2561 2567 2568 2569 2570 2571 2572} proved successful in the majority of cases so treated, but it is frequently followed by intense intercostal neuralgic pains which are apt to persist over long periods of time. Equally good results were obtained by French workers^{24 2027} from novocaine infiltration of the preaortic plexus. The most dramatic and lasting improvements, however, are achieved by direct surgical intervention on the sympathetic system (Fig. 56). Some of the first methods of this kind were introduced by the Roumanians Junnescu¹⁰⁷¹ and Danielopolu^{1053 1054}. According to the traditional trend of thought with its complete disregard of the myocardial hypoxiating activity of the efferent sympathetic fibers, such operations were hitherto conceived in principle as being effective only by interrupting the afferent, pain-carrying pathways or some allegedly coronary constrictor sympathetic fibers. It is true that the former purpose is actually being fulfilled^{1714 1722} by cardiac sympathectomy. However, it was overlooked that all of these procedures (with the exception of those limited to the dorsal roots,^{2736 2513}) eliminate not only the pain-conveying but also a pain-producing mechanism. As far as they concern the stellate ganglion^{1053 1054} and the first four thoracic ganglia^{1057 1224 1244 2554 2562 2573 2574} or their post-ganglionic ramifications²⁷¹⁹ down to the pre-aortic⁷¹ and pericoronary nerve plexus^{731 733}, they include the efferent nervous elements⁵⁰⁷, which are responsible for the liberation of catecholamines into the myocardial cells, and thus for the origin of hypoxia and of pain which is then signalled back to the brain over afferent pathways (Fig. 58a, b).

Additional evidence for this concept was obtained by Cannon and Lissak¹⁰⁵, by Barq¹¹, by the writer in collaboration with the late Dr J. P. Mac²⁷¹⁴ and by Goodall¹²⁰⁴ through the finding of a marked reduction of the

of primarily local metabolic processes in the heart muscle itself under direct hormonal-neurohormonal influence.

The possibility cannot be denied that alterations of peripheral metabolism may lead to significant regulatory repercussions on the part of cardiac action, mediated both by reflectory neural and by humoral mechanisms. Yet, the lack of a demonstrable, clear, quantitative or time relationship between the behavior of the basal metabolic rates after thyroid inactivation on one hand and the improvement or disappearance of the clinical features of angina pectoris on the other^{250, 2679, 2680, 2952}, makes a prevailing extra-cardiac mechanism of the therapeutic effect of thyroid inactivation more than doubtful. Leblond and Hoff¹⁹⁴⁸, Rasmussen²⁷⁴⁵, Somerville and Levine²²⁰¹, and others (p. 35) have also stressed the immediate metabolic action of the thyroid hormone on the heart muscle against the concept of an indirect influence via the general metabolism.

Extensive physiological studies (p. 35 ff.) have made it most probable that the thyroid hormone exerts its dynamically and metabolically stimulating action on the heart by potentiating the biochemical, ultimately hypoxia-producing effectiveness of the adrenosympathogenic catecholamines, which are always present in the myocardium.

Shambaugh and Cutler³¹⁰⁰ were the first clinicians who, in connection with a discussion of the mode of action of thyroidectomy in angina pectoris, perceived in 1934 the fundamental importance of epinephrine effects in the pathogenesis of this disease. Their conclusions remained almost unnoticed and are hardly ever quoted in the literature.

Today there seems little doubt left that hormonal interference on the part even of the normal thyroid gland, contributes significantly to the pathogenesis of angina pectoris by potentiating the hypoxia-producing local activity of the adrenosympathogenic catecholamines in the heart muscle whose sclerotic coronary arteries are incapable of adequate dilatation.

Treatment

In view of the dual pathogenic basis of the ordinary forms of angina pectoris, namely (1) coronary stenosis, and (2) acutely hypoxiating chemical interference in myocardial metabolism, there are two primary therapeutic goals to be considered. One concerns the improvement of myocardial vascularization, the other the prevention of neurohormone-induced hypoxia.

Rather heroic surgical procedures for the purpose of establishing new collateral vascular supplies to the heart muscle^{192, 194, 2146, 2351} and of favoring the dilatation and further development of pre-formed capillaries²⁵⁷ proved effective in a number of instances but are of minor interest for our present discussion and can hardly be considered as methods of primary choice.

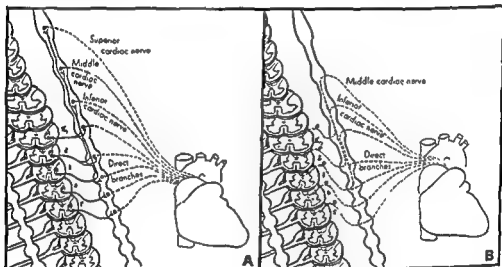
pre-existing hypertension, (b) an electrocardiogram, indicating myocardial damage with cardiac enlargement, (c) cardiac insufficiency. Danielopolu's⁶⁸⁴ condemnation of all techniques, which include stellectomy, is based on the view that the patient's heart should not be deprived of its supply of coronary dilator fibers. However, since the nervous influence on coronary flow is rather insignificant by comparison with the detrimental sympathetic nervous effects on myocardial metabolism (Fig. 49, p. 11 ff)¹⁴¹⁹, this objection can hardly be accepted as justified. The above-listed surgical procedures do not offer merely symptomatic amelioration but can be regarded as effective means to protect the heart from the influx of sympathogenic catecholamines (Fig. 51, p. 377, also Fig. 70, p. 432). What they do not achieve is a restriction of epinephrine discharges from the adrenal medulla. Hence, the incompleteness of their success in a substantial number of cases could be expected.

Theoretically, the application of the so-called *sympatholytic drugs* would appear as an ideal method of non-surgical sympathetic inactivation for the treatment of angina pectoris. Unfortunately, the efficiency of most of these drugs concerning the heart lags far behind that displayed in the peripheral vascular system¹⁴²⁰. The ergotamine alkaloids, with the exception of dihydrogenated compounds, produce simultaneously "musculotropic" effects which are apt to overshadow their beneficial sympatholytic action and which have produced an aggravation of anginal symptoms in several instances^{1966 2032}, even with fatal outcome²²⁹¹. Their use in cases of coronary disease is considered as contraindicated^{2291 2292} despite an occasional normalizing effect on the "anoxic" electrocardiogram^{272 1384 2114 2219 2262 2263}.

Dihydrogenated ergot preparations, such as dihydroergocornine²²⁹², and dihydroergotamine (DHE-45)^{2172 2219}, on the other hand, have been found safe for clinical use. The latter compound was seen to normalize "sympathicotonic" negative T-waves^{1279 2219 2199} and to influence both the clinical status and the electrocardiogram of angina patients favorably²¹⁷². Similar observations were reported with hydergin (CCK-179)^{1572a 2002 2293} in a dosage of 10 to 20 drops three times per day orally over periods of weeks to months. Clinical improvement was seen to begin after 2 to 3 weeks of medication^{1572a}. Schumert²⁸⁰¹ ascribes the therapeutic effect to a normalization of the circulatory dynamic situation and to an improvement of cardiac oxygen economy. Earlier claims that it is possible to differentiate "functional" and "organic" reductions of coronary flow by the response of the electrocardiogram to ergot preparations^{272 249} were not confirmed by other investigators^{1569 2393}.

The benzodioxane compound 883-F was used with some success by

myocardial catecholamine concentration after sympathectomy, (Fig 51, p 377, also Fig. 70, p. 432). Conversely, stimulation of the cardiac sympathetic nerves produced an accumulation of catecholamines in the heart²⁷⁰¹ (Fig 51). Normalization of the electrocardiogram was observed only in a minority of patients²⁰⁴⁶ following cervicothoracic ganglionectomy, but this is undoubtedly due to the fact that mostly severe cases with far advanced coronary stenosis were submitted to such operations. A disappearance of the electrocardiographic characteristics of myocardial hypoxia was also recorded after ganglionectomy, performed with the transthoracic method of Kux^{1974 1975}.



In evaluating the results, obtained in 83 cases of surgical intervention on the upper thoracic sympathetic ganglia and posterior roots, White and Bland²⁵³⁹ arrive at the conclusion that "all suitable cases of angina pectoris can be relieved of their crushing precordial and arm pain by properly executed neurosurgical procedures" but warn against application of these methods in patients with the most advanced forms of coronary disease. Inga Lindgren²⁰⁴⁶, reviewing a series of 105 patients on whom Swedish surgeons had carried out cervicoganglionectomy, reports excellent to fair results in 52.5 per cent of the cases, poor results in 29 per cent, death within one month in 7.5 per cent and nullification of a good symptomatic effect by supervening cardiac decompensation in the rest. Eight patients developed traumatic neuritis. The following points are listed as contraindications: (a) a preceding myocardial infarction which has permanently depressed a

the total dose per series, using 200 kv. (peak), 20 am, 50 cm target skin distance, 1.5 mm Cu plus 1.0 mm Al filter and a field size of 15 by 15 cm. Some of the patients (28 per cent), especially those with co-existing osteoarthritis, received in addition two or three doses of 200 r each through a 10 x 15 cm cone over the cervical and spinal column. The reactions of 200 patients who were treated between 1937 and 1947 are represented in Table 18. The total number of improvements amounted to 76 per cent. Thirty-one per cent of the cases became entirely or almost entirely free from symptoms

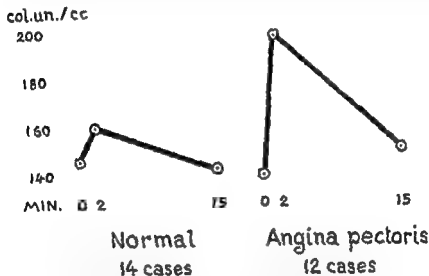


FIG. 50 Average catecholamine concentration in the blood of 14 normal individuals and seven patients with angina pectoris before, two and 15 minutes after a standard exercise test (Method see p. 4, 5)
(After W. Riab, *Ann. Int. Med.* 23: 1010, 1945)

for a recorded average of three and one-half years, with the improvements beginning on an average four weeks following the respective series of treatments. Another 30 per cent were considerably improved for an average of two years, beginning after an analogous average interval. One series of treatments proved sufficient in more than one-half of the best responding cases, while in the others more than one series were required. If no substantial improvement takes place within about eight weeks, it is advisable to repeat the treatments without much delay in order to achieve an optimal cumulative effect. If a patient does not respond satisfactorily after three series of irradiations within a total period of six to eight months, it is useless to undertake any further attempts with this method. More or less intense transitory relapses, some of which were abolished by renewed x-ray treat-

French workers^{536, 5271}. In a few of their cases, a normalization of the electrocardiogram was observed⁵²⁷².

Encouraging results were reported regarding the intravenous application of the *ganglionic blocking tetraethylammonium salts*^{94, 2023}, especially the rapid termination of a status anginosus, whereby normalizations of the ECG were also noted⁹⁴. These drugs must be injected in the recumbent position in doses from 50 mg up, according to individual tolerance. Surprisingly, the beneficial effects seem to persist much longer than one might have expected from the transient action of TEA on the blood pressure (p. 294 ff.) so that only one or two injections per week or every other week sufficed to keep the majority of the patients in a substantially improved condition as long as the treatment was continued^{94, 2023}. Since no permanent relief can be obtained from this form of therapy, and since it is neither very convenient nor devoid of occasional unpleasant side effects⁹⁴, it may prove to be suited only for the immediate alleviation of severe pain in patients who did not respond to other treatments and in whom a myocardial infarction can be ruled out.

In view of the fact that there is reason to believe that not only the discharges of nor-epinephrine from the cardiac sympathetic fibers but also *epinephrine, secreted by the adrenal medulla*, contribute to the pain-producing myocardial hypoxia in patients with coronary sclerosis, particularly during physical exercise, as suggested by the abnormally high rise of the blood catecholamines (Fig. 59), a reduction of adrenal epinephrine discharges appears as another rational goal in the therapeutic approach to angina pectoris.

Animal experiments, carried out by the writer and Dr. A. B. Soule, Jr.²⁷¹⁷, and reports of other investigators^{51, 492, 563}, suggest a depressing effect of x-rays on medullary epinephrine production and secretion (Fig. 56, p. 384).

After an improvement of anginal symptoms in x-ray treated hypertensive patients had been noted as a side effect by Hutton¹⁸¹³ as early as 1935, systematic attempts to treat angina patients with x-ray irradiation of the adrenal region were undertaken by the writer and Dr. E. Zdansky in 1937. The results proved encouraging enough to test this method on a larger scale which was continued in the United States in association with Drs. A. B. Soule and F. Van Buskirk^{2661, 2663, 2659, 2718}. Each series of treatments, with a few exceptions, consisted of six single exposures of the adrenal areas on consecutive days, alternately of the right and left side, each dose being 200 r, measured at the skin. Thus, each area was given 600 r as

Ad (a) Neither in the writer's own series nor in those of other workers, thus in a total of approximately 500 cases (see below), did any untoward reaction on the part of the adrenal cortex occur. The failure of the blood

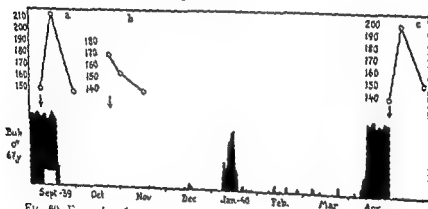
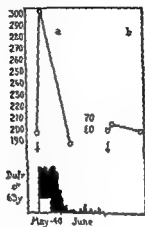


FIG. 61. Treatment.

pressure to become significantly depressed either in normotensive or hypertensive individuals is in agreement with this experience.

Ad (b). Objective evidence of the biological effectiveness of the treatment is available from the writer's observation that the abnormal catecholamine discharges into the blood which occur in angina patients during exercise were reduced in successfully treated patients but reappeared in case of recurrence of the symptoms (Figs 60 and 61). Moreover, normalizations

ment, occurred in 10 per cent of all cases; full strength and probably permanent relapses were reported in 23 per cent, but in reality the percentage must undoubtedly have been higher, as contact with the patients was lost in many instances.

By comparison with other statistics concerning duration of angina pectoris until death^{25,28}, no claim can be made of a life-prolonging effect nor of a prevention of infarctions through x-ray treatment over the adrenals.

Nothing definite can yet be said concerning the value of the combination with treatments over the cervical and thoracic spine, but it should be mentioned that x-ray irradiation of the chest or spine alone has been applied in angina pectoris by many workers^{25, 199, 1146, 2026, 2240, 2407, 2626, 3122, 3117, 3508} with varying, largely favorable results which are probably attribut-

TABLE 18

Results of X-Ray Irradiation of the Adrenals in 200 Cases of Angina Pectoris
(After W. Raab, Am. J. Roentgenol 63 895, 1950²⁶⁸⁹)

DEGREE OF IMPROVEMENT	NUMBER OF CASES	ANGINA DECLINUS PER GROUP	DURATION OF ANGINA PECTORIS BEFORE TREATMENT (AVERAGE)	NUMBER OF X-RAY SERIES (AVERAGE)	INTERVAL BETWEEN TREATMENT AND MAXIMAL IMPROVEMENT (AVERAGE)	DURATION OF IMPROVEMENT (AVERAGE)
+++	63 (31%)	76%	49%	3.8 yrs.	1.6	43 months
++	60 (30%)		35%	3.7 yrs.	2.1	24 months
+	20 (15%)		52%	3.9 yrs.	2.3	18 months
-	48 (24%)		63%	6.2 yrs.	1.8	—
Total	200 (100%)	49%	4.4 yrs.	1.9	4 weeks	31 months

able to the specific depressant effect of x-rays upon the irritability of nerve cells, as described by Desjardins²²⁵.

No untoward side effects were noted in connection with the x-ray treatments, except for slight to moderate nausea, lasting three to five days in 15 per cent of the cases, and a transitory skin rash over the exposed areas in one case. As a matter of precaution, treatments were postponed for two to three months in patients who had recently undergone a coronary occlusion, and in those who showed signs of cardiac failure, until compensation was restored. In cases of tuberculosis, it may be preferable to resort to other forms of treatment. Otherwise, there are no contraindications.

Three academic objections were raised against the x-ray treatment of the adrenals by critics who were obviously unacquainted with its mode of action; namely (a) that it is dangerous by threatening to produce adrenal cortical insufficiency, (b) that the dosage applied is too small to evoke any biological effects whatsoever, (c) that the improvements achieved are of a purely psychogenic nature.

matter which form of treatment for angina pectoris, namely the often underestimated tendency of this syndrome to improve or even to disappear spontaneously¹³⁹⁴. However, here again the time relation between x-ray treatment and onset of improvement and the high percentage of strikingly beneficial effects as well as their long persistence, seem to preclude spontaneous normalizations as a factor of major significance.

Similar favorable results as those observed by the author were obtained with essentially the same technique by several other workers^{1395, 1396, 1411}. One series of 200 cases of angina pectoris was recently reported by Gruneis¹³⁹⁹ after 10 years of experience with the x-ray

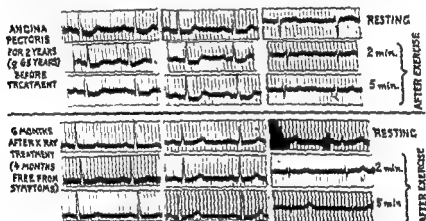


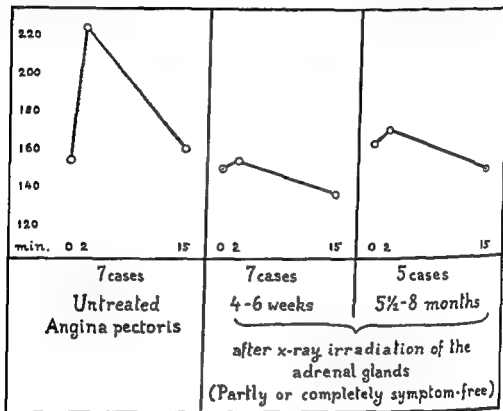
FIG. 62 Normalization of resting and exercise electrocardiograms of a patient with angina pectoris after x-ray treatment of the adrenal glands (After W. Raab and E. Schonbrunner, *Arch f. Kreislaufforsch.* 4: 262, 1939)

treatment over the adrenals. In his summary, the author states that the method gives excellent results. In many cases (75 per cent), a prolonged and in some cases permanent freedom from pain could be achieved. McMillan and Roussau¹⁴⁰² treated 23 patients with severe angina pectoris. In 74 per cent, they achieved "marked relief of pain" and state that "those with greatest disability received more relief than those with less severe symptoms". Scherf and Boyd¹³⁹⁷ found that "in more than 20 personally observed cases the results were satisfactory and seemed to go definitely beyond the individual variations in the course of the

... may for a long time" and the effect was "an immediate one in seven cases" (13). In one of these cases, a normalization of the ECG which had been

of both the resting and exercise ECG were noted by several observers 1327, 1566, 2716 in some of the successfully treated cases (Fig. 62).

Ad (c): A certain participation of psychogenic influences in the clinical improvements obtained by x-ray therapy cannot be ruled out. However, it appears very unlikely that such factors should have played a decisive role, for the following reasons: in most cases the improvements were not



(After W. ARND, *Arch. int. med.* 1930, 40, 222.)

felt earlier than several weeks after completion of the treatments and in many only after a second or third series had been administered. Furthermore, it seems improbable that a purely "imaginary" disappearance of previously intractable attacks should persist for months and years. Only four out of 23 improved European patients who lived through prolonged periods of extreme excitement, tension and fear suffered lasting recurrences of their anginal symptoms.

A perhaps more reasonable objection would be one which can be held with equal justification against all reported successes, achieved with no

Cronbach¹²² that "we are frankly skeptical of these results,

employment." Inconclusive results, obtained by treatment in six patients, treated with one series and two patients having received two series, are summarized by these authors as follows: "We cannot state that such therapy has no benefit, but as far as we proceeded with it, there was not sufficient promise of merit to justify its continuation."

On the basis of his own extensive experience, the writer is convinced that the method in question is both rationally founded and safer, more lastingly effective, more convenient and less expensive than any other among the long-range forms of non-surgical therapy for angina pectoris, with the possible exception of radio-iodine (see below). However, he reiterates his plea, also voiced by others^{123, 124, 125}, that the method be given a fair trial by some of the large clinical institutions where a close follow-up of the treated patients and a critical comparison with the effects of sham treatments would be feasible in sufficient numbers of cases.

Total ablation of the normally functioning thyroid gland was introduced as a therapeutic method for angina pectoris by Blumgart, Levine and Berlin in 1933¹⁰¹ (Fig. 56, p. 334). It has been superseded by equally effective non-surgical methods (see below) but still retains its historic significance as an important landmark on the way to the recognition of the biochemical nature of angina pectoris. Satisfactory and, in part, excellent results were obtained with this procedure by a number of workers^{126, 127, 128, 129, 130, 131} with varying degrees of improvement in 80-90 per cent of 133 patients, among whom the operative mortality was 3.75 per cent¹²⁸. According to a collective review, published in 1939¹³², the total percentage of marked or moderate improvements in 218 cases was 83 per cent. Maximal amelioration used to persist in those cases in which the basal metabolism was kept at the level of ~ 20 per cent (if necessary by means of thyroid medication to combat myxedema)^{129, 133}. The symptoms disappeared frequently before a significant change in general metabolism had taken place^{134, 135}. This was tentatively ascribed to unintentional injury of afferent sensory pathways¹³³. However, such an auxiliary hypothesis is unnecessary if one does not consider the final therapeutic effects as dependent on general metabolism but rather on the metabolic situation within the myocardium itself, resulting from a reduced hypoxiating effectiveness of the adreno-sympathetic catecholamines. One group of workers noted a diminution of epinephrine sensitivity (concerning blood pressure and heart rate) after thyroidectomy only when frank myxedema had developed¹³⁴. They denied its significance for the clinical improvement therefore. This argumentation cannot be ac-

persistently pathological for four years accompanied the subjective improvement (Fig. 63)] "In severest cases of status anginosus, we achieved the best results with roentgen irradiation of the adrenal glands"²⁶¹. "I would recommend unconditionally irradiation therapy to every patient with angina pectoris"³⁰⁰⁷.

No definite explanation can be offered for the complete failure to respond to the treatments in about one out of every four cases. Neither age nor symptomatic severity is a criterion which would permit a prediction of

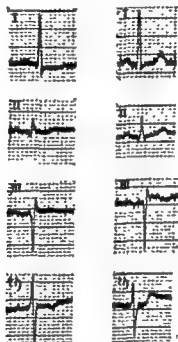


FIG. 63 In a patient with severe angina pectoris, the depression of S-T and T which had existed for four years disappeared together with the clinical symptoms after x-ray treatment over the adrenals
(After W. Hadorn, Arch f. Kreislaufforsch. 2 1, 1937)

success or failure. Cases of long standing and those with angina decubitus seem to give a somewhat less promising outlook than others. This suggests that the degree of coronary sclerosis might play a role. Besides, there may be differences between those cases in which the attacks are caused chiefly by discharges of epinephrine from the adrenal medulla and those in which catecholamine discharges from the cardiac sympathetic fibers prevail. The latter would have to be expected to be less responsive to irradiation of the adrenals.

Against the above-mentioned observations, which showed clinical improvement in approximately 75 per cent of a total of approximately 500 patients treated with x-ray irradiation over the adrenal glands, stand the

TABLE 19

Results of Treatment of Angina Pectoris with Thiourea Compounds

TYPE OF DRUG	AUTHORS	NUMBER OF CASES TREATED	NUMBER OF CASES IMPROVED	% OF CASES OF GROUP IMPROVED	DEGREE OF IMPROVEMENT				BEGINNING OF IMPROVEMENT AFTER NO. OF WEEKS (AVERAGE)	NUMBER OF CASES WITH SIDE EFFECTS*
					+++	++	+	-		
Thiouracil	Raab ¹⁸⁶⁰	11	9	82	5	3	1	2	4	0
	Ben Asher ¹⁹⁰⁹	8	8	100	2	5	1	0	4	0
	Reveno ¹⁹²²	8	5	62	3	2	0	2	7	0
	DiPalma & Nagovero ¹⁹²⁴	8	4	50	2	0	2	4	3	3
	Fisher & Zukerman ¹⁹²⁷	16	14	88	?	?	?	2	2	7
	Sznabrin ¹⁹²⁷	2	2	100	2	0	0	0	?	0
	Ben Asher ¹⁹²⁸	37	25	67	7	13	5	12	3	8
Propyl-thiouracil	Hollander & Mandelbaum ¹⁹²⁹	10	4	40	1	2	1	6	8	5
	Raab ¹⁹²⁹	9	7	78	1	3	3	2	10	0
	Ben Asher ¹⁹³¹	32	12	38	0	7	5	20	3	2
	Waitzkin ¹⁹³²	7	5	71	2	1	2	2	11	0
Methyl-thiouracil	Schoenewald ¹⁹³³	3	3	100	1	2	0	0	7	0
	Frisk & Lundgren ¹⁹³⁴	9	8	89	4	3	1	1	13	1
	Sniehotta ^{1934a}	19	15	78	?	?	?	4	1	0
	Baur ¹⁹³⁴	14	10	71	?	?	?	4	?	0
Thiouracil, Propyl-thiouracil, Methyl-thiouracil	Kienle ¹⁹³⁵	11	8	73	6	2	0	3	4	0
	Moia & Bronstein ¹⁹³⁵	1	0	0	0	0	0	1	?	1
Methyl-thiouracil	Pereira & Figuerredo ¹⁹³⁵	■	?	78	6	0	1	2	?	0
Total		214	146	68	42*	43*	21*	67*	45	23 (13%)

* Incomplete number because of lack of details in some of the reports

** Including leukopenia, skin rash, drug fever, edema, dyspnea, headaches, gastric distress, but not myxedema

In order to obtain prolonged relief from symptoms for periods of several months or years after discontinuation of treatment, it was found necessary to continue the medication uninterruptedly for about 12-18 months. Trans-

cepted (a) because the circulatory features tested are essentially irrelevant for the mechanism of anginal pain, and (b) because indications for a diminution of the effect of epinephrine on the electrocardiogram²⁶⁷ and for a diminished ability of injected epinephrine to produce anginal symptoms¹³⁸ have been obtained after thyroid inactivation regardless of the level of the basal metabolism and the rate of blood flow.

The serum cholesterol of all thyroidectomized cases of one series rose to levels of about 300 mg per cent, ascending occasionally as high as 543 mg per cent¹¹⁵¹.

Because of the inherent hazards and inconveniences of the surgical intervention, and because of the irreversibility of the loss of the thyroid gland which often necessitated substitutive thyroid medication, thyroidectomy was abandoned as a method of choice for the treatment of angina pectoris after about five years of trial.

The logical next step suggested itself with the advent of "*chemical thyroidectomy*" by means of thiourea compounds. It was undertaken simultaneously and independently by the writer²⁶⁵⁰ and by the late Dr. S. Ben Asher²⁰⁹. Using thiouracil^{209, 210, 297, 1767, 2650, 2655, 2752, 2927}, propyl-thiouracil^{211, 1543, 2561, 2657, 2419}, and methyl-thiouracil^{174, 1078, 1767, 3022, 2156a}, a number of authors achieved favorable therapeutic results (Table 19) in an average 68 per cent of the 214 cases recorded up to date.

The daily dosage of thiouracil (which is no longer being used because of its potential toxicity) ranged between 400 and 1000 mg, that of the much less toxic propyl- and methyl-thiouracil between 100 and 3000 mg, but doses higher than 300-500 mg are only rarely to be recommended.

The time of onset of clinical improvement varied widely between one week and four months of continuous medication, with an average of four and one-half weeks. The propyl- and methyl-thiouracil compounds appeared to be slower in action than thiouracil proper but ultimately not less effective. According to one report²¹¹, a markedly lesser efficiency of propyl-thiouracil was observed but this difference was undoubtedly caused by the rather low propyl-thiouracil dosage applied in this particular series.

It has been claimed that the treatment with thiourea compounds is ineffective in patients with an originally low basal metabolism⁷⁵⁶. This statement is unfounded, as evidenced by many instances which prove the contrary²⁶⁵⁷. Normalization of the ECG^{1767, 2650, 2657} (Figs. 64, 65), and an increase of exercise tolerance^{1078, 2419} and of hypoxemia tolerance¹⁰⁷⁸ were observed in some of the favorably responding cases. Objective evidence of the efficacy of thiouracil medication was furnished by the writer²⁶⁵⁰ by inserting periods of placebo administration during which the anginal symptoms used to return in full force (Fig. 66).

as a disturbing side effect. No damage to the bone marrow seemed to have occurred in any of the propyl- and methyl-thiouracil-treated patients; but the writer insists, nevertheless, on frequent blood counts during medication. This latter inconvenience, the undesirable cholesterolemia and the occasional tendency toward edema formation, furthermore the slow development of the improvements and the limited duration of effectiveness constitute disadvantages which, in the writer's opinion, make the treatment with thiourea compounds definitely inferior to the x-ray therapy over the

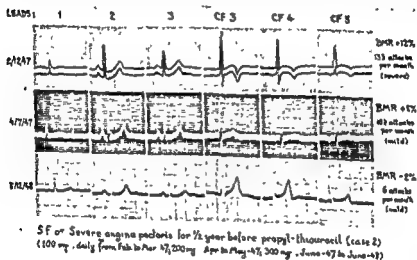


FIG. 65
pectoris in
curves retr.

adrenals. The paradoxical fact that it has aroused so much more interest and favorable comment among other workers than the x-ray treatment is probably due to the psychological preference of most cardiologists for a therapy which they can carry out themselves without the necessity to enlist the collaboration of a roentgenologist.

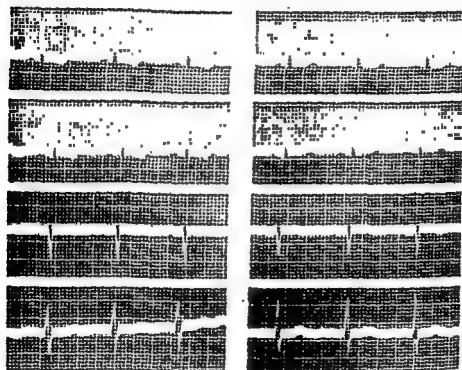
Combined irradiation of the adrenals and thiouracil treatment were applied with dramatic and complete success, lasting 5 years up to the present, in one case of excruciating status anginosus. It will be wise, however, to be particularly watchful in the case of such combined treatments concerning the reaction of the white blood picture because of the simultaneous exposure of the bone marrow to two potentially noxious influences.

Some of the shortcomings of both thyroidectomy and the antithyroid drugs are circumvented by the application of radioactive iodine (I^{131}), as

ient symptomatic improvements were seen in patients with rheumatic lesions of the aortic valves and severe nocturnal attacks of anginal pains²⁸⁴.

No clear-cut relationship was found by most observers between the quantitative changes of the basal metabolic rate and the clinical reaction of the individual patient, although deeper depressions of the basal metab-

E.P. ♀ 63 YRS. ANG. PECT. FOR 7 YEARS.



UNTREATED
SEVERE ANGINA

B.M.R. +24%

THIOURACIL (2 weeks)
ALMOST SYMPTOM-FREE

B.M.R. +9%

FIG. 64 Normalization of the electrocardiogram of a patient with severe angina pectoris by thiouracil, paralleled by marked improvement of symptoms (After W Raab, *Ann Int Med* 28 1010, 1948)

olism and appearance of myxedema were more frequently accompanied by symptomatic improvement.

Supervening myxedema is easy to control by temporary discontinuation or diminution of the dosage. Increases of the serum cholesterol level were noted with great regularity. In one case observed by the writer²⁶⁵, it reached 506 mg per cent. Reduction of the dosage is soon followed by normalization.

In a few isolated instances, generalized edema^{756 1549 2261} was produced

recently advocated by Blumgart and co-workers^{200a, 201}. The administration of 26 to 206 millicuries in single or divided doses produced excellent results in 9 out of 26 cases of angina pectoris, worth-while results in 10 and no effect in 7 during a follow-up period of 12-40 (average 24) months. Similarly favorable responses have been reported so far by two other groups of workers^{144a, 145a} in 28 and 29 patients respectively. Out of all 83 cases, 43% gave good to excellent and 29% fair or "worth-while" results.

No toxic side effects were noted, except for a mild thyroiditis, lasting a few days, in about two thirds of the cases. Thus, this form of treatment seems to be about equal in efficiency, immediate safety and duration of effect, to the x-ray irradiation of the adrenals. Blumgart and Freedberg^{200a} list as contraindications: hypothyroidism, cardiovascular syphilis, malignant hypertension and the terminal stage of severe angina. Best results were observed at a BMR level of -20 to -25% which may have to be maintained by daily medication with 6-30 mg of thyroid hormone. The hazards, inherent in the production of permanent hypothyroid hypercholesteremia regarding the progression of coronary atherosclerosis (p. 39) will have to be evaluated on the grounds of long-range statistics.

Among the instantaneously acting short-range forms of treatment, the application of nitrites, notably of nitroglycerine, is well enough known not to require any detailed discussion of its practical use. However, one point

influence of nitroglycerine on the metabolism of the heart muscle. A significantly augmented oxygen saturation of the coronary venous blood was seen during nitroglycerine action^{101a}. The cardiac output was found markedly decreased in most cases of angina pectoris by this drug^{200c}, but increments were observed in others^{200d, 212a}. Stroke volume^{270a, 207a, 212a} and radiographic heart size^{270a, 1551a} are reduced by nitroglycerine and other nitrites. The appearance of electrocardiographic changes during exercise could be prevented through nitroglycerine intake^{200c, 239a}. In humans and in animals, the hypoxic electrocardiographic effects, elicited by epinephrine^{24, 210a, 209}, nor-epinephrine and cardiac sympathetic stimulation²⁰² were blunted at

of nitroglycerine with the exaggerated myocardial oxygen consumption under the influence of epinephrine could be demonstrated in dogs²²⁵ (in contrast to the rat²²⁷). However, a diminution of oxygen consumption of

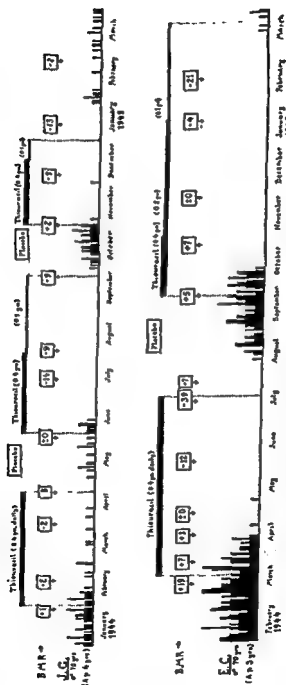


Fig 56 Thioaural treatment in two patients with angina pectoris, interrupted by periods of placebo administration. Severity and frequency of attacks indicated by vertical black bars (After W. Rumb, J A M A 128: 219, 1945)

vascular tissue under the influence of nitrites¹⁷⁹ and the other above-mentioned experimental observations suggest the probability that the nitrites produce their immediate beneficial effects in angina pectoris not only by coronary dilatation (for which sclerotic vessels are poorly suited anyhow) but by an antagonistic action either against the catecholamine-induced hypoxia of the heart muscle per se or against the pain-producing unoxidized metabolites in the myocardium. In arterial tissue the nitrites were found to interfere with the activity of adenosinetriphosphatase¹⁸⁰.

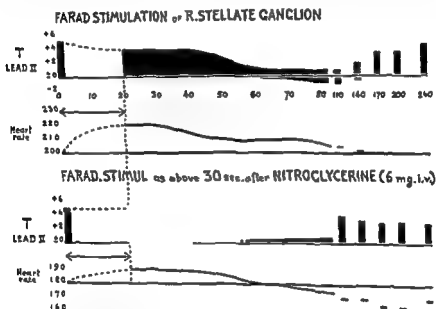


FIG. 68. Abolition of the cardiac sympathetic stimulation-induced depression of the T-wave by nitroglycerine i.v.
(After W. Raab and E. Lepeschkin, *Circulation* 1:733, 1950)

ac

v2

in patients with "coronary insufficiency" in whom the electrocardiographic effects of inhalatory hypoxia and the tendency to develop anginal pain during low oxygen breathing were diminished¹⁸¹. Clinical improvements of the anginal syndrome, both immediate and prolonged, have been reported by German workers^{182, 183, 184, 185, 186} and by B. Kisch¹⁷⁷. The dosage is in the beginning 0.1 mg per day intravenously, with gradual augmentation to 0.3 or 0.4 mg per day and continued treatment for four to six weeks¹⁸¹. No digitals must be administered simultaneously or for about two weeks before strophanthin medication.

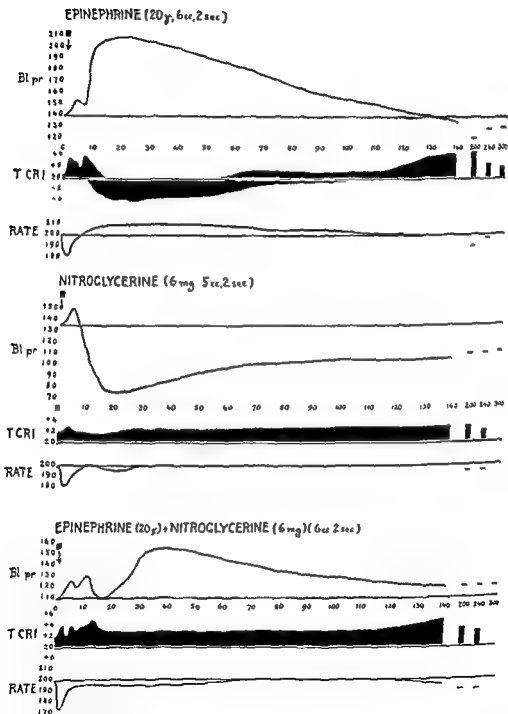


FIG. 67. Abolition of the epinephrine-induced inversion of the T wave (in the atropinized cat with adrenals tied) by nitroglycerin i v. For explanation of T-wave amplitude curves, see legend to Fig. 3.

(After W. Raab and L. Lepeschkin, *Circulation* 1:733, 1950)

extraneous and hemic oxygen supply seems to preclude impressive therapeutic effects

Acute stimulation of the vagus by pressure on the carotid sinus as recommended by Levine²⁹⁹, was also frequently used in the clinic of the late Professor Wenckebach to terminate violent anginal attacks, with occasionally striking immediate results. It is a logical procedure since it can be assumed to initiate promptly an antiadrenergic, chemically oxygen-sparing vagal effect upon myocardial metabolism (p 374, Fig. 49). Conversely, atropine in large doses, by permitting adrenergic prevalence, was seen to aggravate anginal symptoms³⁰⁰ and to provoke severe hypoxic alterations of the ECG²⁹⁸. The latter could be normalized by nitroglycerine, presumably by the same mechanism which counteracts the hypoxic changes, induced by injected sympathomimetic catecholamines.

Papaverine is an effectively vasodilating drug^{301-304, 344}. It is also capable of markedly diminishing catecholamine-induced tachycardia³⁰¹ and the electrocardiographic changes which develop during exercise (one case)³⁰³. Nevertheless, it was not found to produce unequivocally beneficial effects in angina pectoris^{3108-3110, 3148, 3234}, although earlier reports had claimed favorable results from the administration of large doses^{377, 381}.

Among the short-range types of treatment for angina pectoris, application of the powerful coronary dilator, khellin⁴³ seems to be particularly effective. Improvements concerning the number and severity of attacks, exercise tolerance and electrocardiographic changes^{43, 219} have been observed in an average 81 per cent of more than 550 cases reported up to now^{43, 725, 731, 2187, 2463}. Alternating placebo medications were accompanied by recurrences of the symptoms^{43, 219}. The drug is administered orally as a rule (50 mg three or four times daily in the beginning, followed by a maintenance dosage of 50-150 mg per day, up to 200 mg per single dose may be given in acute episodes). By the intramuscular route, the daily dosage is 50-100 mg. Improvement becomes noticeable within three to 10 days. Excretion of the drug is slow. Nausea, vomiting, vertigo, dizziness, restlessness are the most common side effects. The drug may be used as a purified crystalline preparation.^{3039a}

In view of its extraordinarily potent dilating action on the coronary arteries, khellin, like nitroglycerine, is unanimously believed to exert its therapeutic effect by this mechanism alone. Yet, as long as myocardial metabolism has not been studied under the influence of this interesting substance, its clinical effects cannot be accepted as definite proof of a purely vascular mode of action.

Cytochrome C was believed to be suitable for the treatment of angina pectoris by increasing the myocardial oxygen uptake because it prevented the electrocardiographic changes induced by inhalation of 10 per cent oxygen²⁶⁴, and occasionally improved an abnormal electrocardiogram²⁶⁴. However, it does not seem to have fulfilled the expectation of clinical

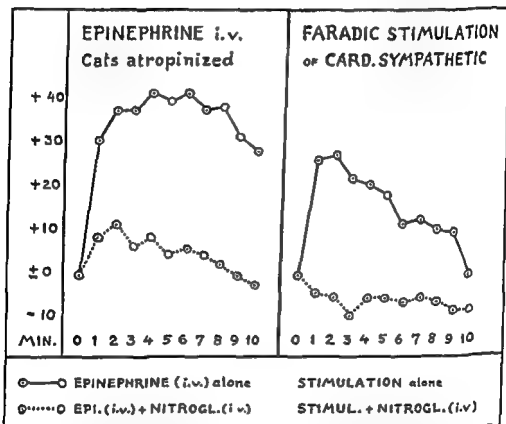


FIG. 99 Counteraction of nitroglycerin against cardiac acceleration elicited by epinephrine injection or stimulation of the cardiac sympathetic
(After W. Raab and R. J. Humphreys, *Ann. Int. Med.* 28: 1010, 1948)

usefulness^{123, 273, 280}, perhaps on account of the presumable fact (p. 373 ff) that myocardial oxygen uptake and consumption are already at a maximum during the anginal attack, the basis of which is not so much extrinsic oxygen lack as intrinsic oxygen wastage.

Inhalation of oxygen, although apt to somewhat increase working capacity²⁸¹ and to improve occasionally the hypoxic electrocardiogram of angina patients²⁸², does not produce any marked beneficial results and cannot be considered as a practicable procedure^{280, 283}. Here, too, the quantitative prevalence of intramyocardial oxygen wastage over minor variations of

different types of treatment may be largely attributable to coronary stenosis of such an advanced degree that the "coronary reserve" is practically exhausted and the slightest increase of myocardial oxygen consumption will call forth painful hypoxia.

The possibility of rational therapeutic intervention with a fair prospect of prolonged effectiveness, exists in the majority of patients with angina pectoris, including many with severest subjective symptoms. The bewildering variety of procedures offered in professional publications and the many, often, irresponsibly exaggerated reports appearing in the lay press may be the main reasons for the distrustful attitude of most practicing physicians who prefer to adhere to the old palliative routine of nitroglycerine and aminophylline rather than to expose their patients to any of the suspicious "new-fangled" therapeutic methods. More time and much more systematic work will be needed to establish a solid foundation for the practical choice of the most promising, safest and least expensive forms of treatment to be applied singly or in suitable combinations, and to overcome the inertia of those who refrain from action with the convenient excuse that the patient should be kept in possession of his allegedly desirable painful anginal "warning signals". The writer does not subscribe to the widespread worship of longevity at all costs and rather favors the relief from sufferings which are still unnecessarily imposed upon countless angina patients by their ultra-conservative or inadequately informed medical guardians.

Summary

The symptoms of angina pectoris in patients with coronary sclerosis cannot be explained satisfactorily by the traditional mechanistic concept which maintains that myocardial hypoxia results solely from a diminished coronary flow in combination with increased cardiac work, since neither a direct quantitative nor time relationship exists between myocardial dynamic performance and the occurrence of anginal pain in such patients. Any interpretation of the pathogenic mechanism of angina pectoris which does not take into account the chemical effects of acute adrenergic discharges from the cardiac sympathetic nerves and the adrenal medulla on myocardial metabolism, is incomplete.

The most important physiological fact whose realization is indispensable for the understanding of the occurrence of myocardial hypoxia under the influence of sympathetic stimulation (e.g., during exercise, exposure to cold and emotions), is the excessive and wasteful consumption of oxygen by the heart muscle, elicited by the adrenosympathogenic catecholamines nor-epinephrine and epinephrine. It leads to myocardial hypoxia if unopposed by oxygen-sparing cholinergic counteraction and it occurs in principle regardless of myocardial work and of coronary flow as a specific chemical

A moderate coronary dilatatory effect is generally attributed to various xanthine compounds, especially *aminophylline*, but these claims have not remained uncontradicted. Studies with the catheterization technique in intact animals did not reveal any effect on coronary flow and the coronary venous oxygen unsaturation was increased in contrast to the opposite effect of nitroglycerine^{1015, 1745}. Although the act of prescribing theobromine preparations or aminophylline has assumed the character of a conditioned reflex among many physicians, its real clinical value is still a matter of controversy^{1060, 2407, 2512} and the writer has long ago given up its use, except for an occasional intractable case, *ut aliquid fieri videatur*.

Reports concerning beneficial effects of the administration of *testosterone propionate*^{337, 1355, 1979, 2596, 3140, 3303, 3190, 3193} and other male sexual hormone preparations^{63, 1467} in patients of both sexes with angina pectoris, are viewed with skepticism by some authors^{1990, 1993, 3313}. However, they do not appear inconceivable in the light of observations which showed that characteristic metabolic changes, analogous to those, produced by epinephrine, and occurring in the heart muscle of castrated animals, could be abolished by administration of the male sexual hormone³⁰¹⁹ and that even in relatively young men with angina pectoris the total urinary steroid excretion may be significantly diminished¹¹³⁰. In 179 (74 per cent) out of a total of 242 published cases, clinical improvements were reported concerning exercise tolerance, nitroglycerine requirement and general well-being. A partial normalization of the electrocardiogram was only sporadically seen³¹⁹⁰, however. The duration of the clinical effects after discontinuation of treatment varied between two and 34 months¹⁹⁷⁹. The usual dosage of testosterone propionate per intramuscular injection is 25 mg. As a rule, the treatments were begun with two to three injections per week and continued with one weekly injection until an average of 12 doses had been administered¹⁹⁷⁹. Some authors warn against over-dosage because of the undesirability of a stimulated *libido*.

The question of a therapeutic usefulness of *Vitamin E (alpha-tocopherol)* in angina pectoris was handled from the beginning under unfortunate circumstances which rendered an objective evaluation difficult. The enthusiastically favorable statements made by the initiators of this treatment^{64, 3133, 2194, 2407}, have so far not been confirmed by a number of other workers^{115, 125, 1997}. Metabolic effects of vitamin E on the myocardium were ascertained experimentally³¹³⁴, but in which way they might be correlated with those underlying the anginal syndrome, cannot be decided at the present time.

A survey of the various therapeutic procedures for angina pectoris shows that by the application of several of them at least some degree of prolonged improvement can be achieved in approximately 75 per cent of the cases treated (Table 20). The non-response of about one out of four patients to

TABLE 20—continued

MODE OF ACTION	METHOD	APPROXIMATE NUMBER OF CASES TREATED	APPROXIMATE PER- CENTAGE OF NUMBER OF CASES REPORTED IMPROVED	REPORTED DURATION OF IMPROVEMENT	SIDE EFFECTS
Desensitization of myocardium to hypoxia-producing catecholamines through thyroid inactivation	Thyroidectomy (total)	218	83%	Months to years	Myxedema; Hypercholesterolemia; Fatalities
	Thiourea compounds	214	65%	Weeks to years	Hypercholesterolemia; leukopenia; edema, dyspnea
	Radioactive iodine	83	72%	Months to years	Myxedema; hypercholesterolemia, transient thyroiditis
Coronary dilatation plus apparent counteraction against metabolic effects of catecholamines in the heart muscle	Nitrites	Indefinite	Almost 100%	Minutes to hours	Dizziness, Headaches
	Khellin	450	75-90%	Days	Nausea; Drowsiness, Insomnia
Improvement of myocardial oxygen economy	Strophanthin	370	80%	Weeks to years	None, unless overdosed
Normalization of myocardial intermediary metabolism (?)	Testosterone propionate	240	74%	Months to years	Excessive libido, virilization

anatomical lesions of the coronary arteries It makes the unproven hypothesis of a "coronary spasm" superfluous. Whether hypoxia per se or the accumulation of unoxidized metabolites (lactic acid) in the heart muscle constitutes the ultimately pain-eliciting factor cannot be decided at this time.

The thyroid hormone contributes significantly to the biochemical mechanism of angina pectoris by markedly intensifying the hypoxia- and pain-producing local effects of the adrenosympathogenic catecholamines on the heart muscle, regardless of its influence upon peripheral oxygen consumption.

TABLE 20
Therapeutic Procedures for Angina Pectoris

MODE OF ACTION	METHOD	APPROXIMATE NUMBER OF CASES TREATED	APPROXIMATE PER- CENTAGE OF NUMBER OF CASES REPORTED IMPROVED	REPORTED DURATION OF IMPROVEMENT	SIDE EFFECTS
Re-vasculariza- tion of heart muscle	Cardio-myopexy Cardio-omentalopexy Ligation of coronary sinus Artificial pericarditis	132	68%	Months to years	High mor- tality
Severance of af- ferent, pain- conveying path- ways	Posterior rhi- zotomy	57	86%	Months to years	High mor- tality
Simultaneous in- activation of afferent, pain- conveying and efferent, neuro- secretory, pain- producing (hy- poxia-evoking) fibres	Chemical sym- pathetic block (para- vertebral or pre-aortic)	160	75-84%	Weeks to years	Neuralgias; Fatalities
	Cervico-tho- racic gang- lionic or postgangli- onic sym- pathectomy	200	70-100%	Months to years	Neuralgias, Fatalities
	Tetraethyl- ammonium salts (TEA)	39	89-100%	Days to months	Orthostatic hypotension; Nausea
Reduction of epi- nephrine dis- charges from adrenal medulla	X-ray irradia- tion of adrenal glands	500	75%	Months to years	Slight nausea

process. Its hypoxia-producing effectiveness is of course aggravated by coronary stenosis. Exhaustion of the "coronary reserve" and appearance of pain depend jointly on (a) the degree of catecholamine-induced myocardial oxygen wastage, and (b) the degree of coexisting restriction of the coronary flow. In some instances the first alternative alone prevails in the absence of

Anoxic Myocardial Necrosis (Including Myocardial Infarction)

The subject of anoxic myocardial necrosis which includes that of myocardial infarction will be discussed here from the point of view of its relationship to neurohormonal and hormonal activity, insofar as the latter can be considered as participating in the mechanism of its origin and in some of the secondary features of its clinical course.

Definition and General Principles

The terms "anoxic myocardial necrosis" and, more specifically, "myocardial infarction" denote occurrences of necrosis of portions of the heart muscle which are caused by a discrepancy between local oxygen consumption and oxygen supply of such a degree and duration as to prohibit further viability of the tissue affected.

The exact nature and sequence of the chemical reactions leading to necrosis is not known, but it was found that sections of the myocardium whose arterial supply had been experimentally ligated, contain an excess of lactic acid and decreased amounts of glycogen^{1721 1800}. Identical chemical changes are induced by anoxiating doses of epinephrine^{1801 1810 1811, 1812 1813 1814}. Certain alterations in the electrolyte and water distribution of the affected area make their appearance before any histologic abnormalities become detectable¹⁸⁰⁹. In a minority of instances of myocardial necrosis in which autopsy revealed either entirely normal coronary arteries or vascular lesions which were insufficient to explain anoxia in the involved myocardial area on the grounds of anatomical arterial narrowing alone, other causative factors had to be adduced, such as preceding shock¹⁸¹⁵, hemorrhage, tachycardia, acute heart failure, pulmonary embolism, dissecting aneurysm of the aorta, infections, etc.¹⁸²¹

The typical clinical picture of myocardial infarction per se does not necessarily prove the existence of major anatomical lesions of the coronary arteries nor of any other form of severe mechanical interference with the blood supply to the injured area, even though anatomical changes within the coronary lumen are present in the vast majority of cases. Hence, the clinical term "coronary occlusion" is a prejudicial one and should be replaced by the non-committal "myocardial necrosis" wherever the clinical criteria appear to warrant the latter designation. Blumgart and his associates¹⁸¹⁶ have justly emphasized that "the changes in the myocardium . . .

Some of the most successful forms of therapy can be interpreted as in one way or another preventing or mitigating the catecholamine-induced oxygen wastage and resulting painful hypoxia of the myocardium. The following mechanisms are assumed to be chiefly responsible for clinical improvements: (a) reduction of the influx into the myocardium of neurogenic nor-epinephrine (paravertebral sympathetic block, cardiac sympathectomy, tetrathylammonium salts) and of adrenal medullary epinephrine (x-ray irradiation of the adrenal glands); (b) reduction of myocardial metabolic reactivity to the hypoxiating action of the adrenosympathetic catecholamines by inactivation of the thyroid gland (thyroidectomy, thiouracil compounds, radio-iodine). Furthermore, nitroglycerine seems to counteract the catecholamine-induced alterations of the myocardial metabolism, strophanthin is believed to improve myocardial oxygen economy and there exist indications suggesting a normalizing influence of testosterone on the altered metabolism of the myocardial cells. Whether or not khellin exerts any direct chemical effects upon the heart muscle beside its dilating action upon the coronary arterial walls, remains to be investigated.

Among the non-surgical methods, x-ray irradiation of the adrenals (with or without inclusion of the cervico-thoracic spinal areas) and treatment with radio-iodine seem to offer the best prospects for lasting benefit, technical convenience and freedom from harmful side effects, unless the hypercholesterolemia induced by thyroid inactivation should prove to gradually aggravate coronary atherosclerosis. Surgical procedures should be contemplated only if the above-named and other rational conservative measures have failed.

Omission of the tentative application of the safe modern therapeutic methods with long-range action in severe cases of angina pectoris is no longer justifiable.

intimately connected with a marked diminution of cardiac output of probably reflexory origin (p. 423)

Outright shock develops as a rule during the very earliest stage of the clinical syndrome of myocardial infarction. On the other hand, in many cases the blood pressure remains unchanged for several hours or it may even rise temporarily above its preceding level before the characteristic, more or less rapid decline sets in, which constitutes one of the most revealing signs of severe myocardial anoxia. It is usually accompanied by a diminution of the pulse amplitude. A hypertensive blood pressure may fall to a seemingly normal or even subnormal level where it may remain for hours, days or years before returning to its pre-infarction height. This type of blood pressure depression cannot be considered as shock. It will be discussed on p. 423.

Signs of congestive cardiac failure, especially of the left ventricle, may appear very early or after a few days following the attack. They are manifested by rales at the bases of the lungs, cough, dyspnea, orthopnea, blood-tinged sputum and sometimes full-blown pulmonary edema. The prognosis of cases with pulmonary edema is generally poor. Right ventricular failure is said rarely to occur in connection with a first infarction, but to be more common as a sequel of later attacks.¹⁰⁰

Other early and later features and complications of diagnostic or prognostic significance, such as muffled, distant heart sounds, gastrointestinal symptoms, hiccup, convulsions, fever, leukocytosis, fibrinous pericarditis, elevated sedimentation rate, embolic phenomena, cardiac aneurysm and

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the same applies to the characteristic electrocardiographic signs, caused by ultimate anoxic injury of the myocardium.

Cardiac arrhythmias appear as a fairly frequent complication in cases of myocardial infarction. Auricular fibrillation and flutter are not common, but ventricular extrasystoles occur quite often and are considered as forecasting serious developments.^{111 112} They may lead to paroxysmal fatal ventricular fibrillation.^{111 112}

called experimentally in animals by artificial infarcts.^{113 117} In some cases death results from sudden cardiac standstill.^{111 112} Other forms of death in connection with myocardial infarction are caused by shock, cardiac failure or rupture, pulmonary or cerebral embolism and other more indirect complications.

The mortality rate during the first four to six weeks following infarction episodes was estimated by various investigators as 16.5 per cent¹¹¹, 19 per

depend solely on the extent and duration of the relative ischemia, not on the manner in which they are produced."

The term "coronary failure" has been suggested for instances of prolonged cardiac pain, more intense than ordinary angina pectoris, unresponsive to nitrites and rest, and without objective evidence of myocardial necrosis¹⁰⁴¹. It implies without sufficient evidence a primary temporary derangement of the coronary circulation. Because of the likelihood of a primary neurohormone-induced chemical myocardial hypoxia, similar to that underlying the common forms of angina pectoris, the writer does not see any advantage in placing such episodes into a special category, only because of the greater intensity and longer duration of a process which is probably essentially identical with that causing ordinary anginal symptoms. A distinction from myocardial necrosis, on the other hand, is practically feasible, as a rule, and theoretically justified.

Symptomatology

Although the clinical diagnosis of coronary thrombosis had been made and autoptically verified by Hammer¹³⁵⁸ in Vienna in 1878, and by a few others after him^{1349, 2023, 2160}, the outstanding significance of myocardial infarction and its symptomatology remained almost generally unrecognized until 1912 and the following years when Herrick's classical description^{1472, 1474} aroused the interest of physicians throughout the world and thus ushered in a new era of cardiology.

The primary storm signal of anoxic myocardial necrosis, *substernal pain*, with or without radiations of a similar distribution as in angina pectoris, but often more severe and prolonged over hours or even days, varies greatly in intensity from case to case; indeed, it is often entirely absent, as indicated by the correlation of autopsy findings with the clinical history^{305, 347, 690, 1129, 1904}, especially in cases of gradual fibrotic occlusion of coronary branches. The existence of asymptomatic infarctions and of asymptomatic initial periods after coronary occlusions, introduces an element of uncertainty also in the interpretation of the time relationship between the actual development of myocardial necrosis and the appearance of clinical signs. Nevertheless, abrupt occlusions of major coronary branches by intimal hemorrhage or thrombosis, are, as a rule, accompanied by immediate dramatic clinical manifestations.

Shock with a deep fall of blood pressure, a small, rapid, thready pulse, grayish cyanosis, cold extremities, perspiration and mottling of the skin may occur with or without pain and with or without syncope. Unless it terminates in sudden death, the state of shock can persist for from one-quarter hour to several hours, or even for a day or two. Its mechanism is

■ scab-bearing area of the skin would tear the scab and permit blood to ooze out. The observation of an occasional aggravation or perhaps even provocation of myocardial infarcts by coronary dilating nitrites^{141, 210}, appears compatible with the above-outlined concept.

Ad (c): Disseminated necroses in the subendocardial layers and papillary muscles, which are sometimes found in the absence of coronary occlusion (p. 418), occur predominantly in hearts whose oxygen supply has been more or less handicapped from the beginning by coronary sclerosis and/or hypertrophy¹⁶¹. As far as the latter is concerned, it has been claimed to increase by itself the requirements for blood supply because of a growing disparity between the enlarging myocardial mass and a supposedly inadequate expansion of its capillary network^{179, 212, 213}. Although this argumentation seems to be supported by histological findings, it may require revision in the light of the recent electron microscopic discovery of capillaries, entering the interior of the individual cardiac muscle fibers and thus supplying them from the inside with oxygen and other nutrients¹⁷⁷.

Among the precipitating factors, there are some, such as hemorrhage and deep shock, the hemodynamic effects of which may probably suffice by themselves to impair coronary flow to the point of critical anoxia and necrosis. In others, however, e.g., in paroxysmal tachycardia, pulmonary embolism and acute heart failure, a significant participation of the hypoxiating chemical influence of sympathogenic catecholamine secretion into the heart muscle must be taken into consideration. Finally, there are instances on record in which no precipitating cause whatsoever could be identified¹⁶⁰. In the interpretation of cases of this kind, it is no longer necessary to seek succor in the myth of coronary spasms. Chemically induced myocardial hypoxia is known to result from the administration of epinephrine and from stimulation of the cardiac sympathetic nerves (p. 11 ff.)^{160, 212, 213, 214}, i.e. from catecholamine discharges into the heart muscle. The production of myocardial necroses through injections of epinephrine was observed by many authors^{164, 166, 167, 173, 180, 182, 183, 215, 216, 217}. Moreover, myocardial necroses were elicited in animals by enforced exercise¹⁷⁸ which is accompanied by a myocardial accumulation of catecholamines²⁰² (Fig. 51, p. 377), and by tarabazov's^{161, 211}. In the latter experiments, necroses developed in otherwise normal hearts under the influence of sympathetic stimulation. This makes it all the more intelligible that such lesions occur relatively readily in hypertensive and arteriosclerotic human hearts as a result of acute additional catecholamine-induced oxygen losses beyond the requirements of cardiac work set so. In some instances, the electrocardiographic and clinical signs of myocardial infarction were provoked by the injection of over-doses of epinephrine^{162, 218}. Occasionally, electrocardiograms suggestive of a my-

possibility of a certain protective power of gonadal activity. However, coronary sclerosis is by no means limited to the higher age groups, and myocardial infarctions have been reported in numerous cases (about 5 per cent¹⁰⁶⁰) before the age of 40, even in young individuals and children^{164, 228, 2379, 2432, 2605, 2611, 2712, 3121, 3601}.

As in angina pectoris, there is a striking preponderance of arteriosclerotic coronary disease in males, the sex ratio having been estimated as ranging between 2:1 and 6:1^{151, 190, 2256, 2418, 2418}. The finding of thicker coronary arterial walls with a narrower lumen in male infants as compared with those of females was interpreted as a predisposing characteristic of the male sex⁷⁶¹.

The sex difference in the incidence of coronary disease is largely abolished among diabetic individuals^{1435, 2252, 3306} and among those beyond the age of 60¹⁹⁹⁶. These observations suggest hormonal influences which, however, are undefined as yet.

The endocrine factors, which may be involved in the apparent predisposition of obese individuals to coronary sclerosis^{1035, 3620}, are likewise still a matter of conjecture despite many hypotheses which have been advanced concerning the relation of obesity to presumable dysfunctions of the pituito-adrenal system.

Ad (b): The question as to whether hormonal or neurohormonal influences can be made responsible for the occurrence of the individual attack of coronary occlusion, is essentially identical with the question as to whether such influences are likely to cause the rupture of intramural capillaries and to favor the formation of thrombi.

Unusually strenuous exercise^{200, 212, 420, 430, 929, 1065, 1527, 2239, 2437, 2697} and emotional upsets^{212, 1527, 2529}, although not considered as decisive precipitating conditions by some^{2217, 2252, 2591}, have been reported to precede attacks of myocardial infarction (with or without autoptically verified coronary occlusion) immediately, or within a few hours, in so many instances that a causal connection appears well enough established, regardless of the admitted fact that in the majority of coronary accidents no such precipitating events can be identified^{2217, 2252, 2591}. Other less common but apparently also occasionally contributory circumstances are surgical interventions^{131, 2151, 2301, 2726, 2937} and insulin hypoglycemia^{181, 1143}. All of the above-named conditions are conducive to more or less abrupt sympathetic stimulation and to a concomitant dilatation of the coronary arteries. It seems imaginable that the sudden forceful circumferential traction to which the sclerotic coronary walls with their imbedded fragile giant capillaries are exposed under these circumstances, might cause ruptures of both the thin capillary walls and the brittle ulcerated endothelial layers in a similar fashion as stretching of

Surgical shock and other forms of shock are not infrequently followed by myocardial infarction^{181, 209}. Cardiac sympathetic stimulation which causes both coronary dilatation and myocardial chemical hypoxia, and the peripheral hemodynamic changes which lead to a reduction of coronary flow, can be assumed to contribute to the development of myocardial necrosis in case of shock. They may precipitate partial or complete coronary occlusion on the one hand and enhance the chemical prerequisites for myocardial tissue necrosis on the other.

Neurohormonal and Hormonal Aspects of Sequelae

The establishment of myocardial anoxic injury is sometimes immediately followed by an early phase of adrenosympathetic hyperactivity with temporary maintenance of a normal or elevated blood pressure level^{129, 217-221}, cutaneous vasoconstriction, reduction of peripheral blood flow²⁰⁶, profuse perspiration, tachycardia and hyperglycemia²⁵⁶⁻²⁵⁹.

However, the most important and characteristic hemodynamic alteration resulting from anoxic injury to the heart muscle, is the marked reduction of cardiac output which may persist for several days or weeks. In the presence of primary shock, this may be partially attributable to pooling of blood in the presumably dilated vascular periphery. On the other hand, in the absence of shock and during the following weeks of slow recovery, the diminution of cardiac output^{159-163, 173, 175, 176, 199, 212, 213, 202, 203, 213, 214} is to be ascribed with greatest probability to a reflex mechanism^{169, 222} which involves stimulation of the cardiac vagus and has been identified with the Bezold-Jarisch reflex^{148, 221, 202, 203}. This proprioceptive reflex originates in the heart muscle itself and elicits via the central nervous system a vagal diminution of the stroke volume, retardation of cardiac action¹⁶⁰ and an improvement of myocardial oxygen economy²⁰². It can be put into effect by a variety of chemical influences upon the heart which include, significantly, large hypoxia-producing doses of epinephrine¹⁴⁸. Jarisch¹⁶¹ and Schimert²⁰⁰ are of the opinion that the injured area of the myocardium serves as the starting point for the reflex mechanism in question, which is believed to cause a functional adaptation of the damaged heart muscle to its own diminished dynamic capacities, mainly at the expense of the stroke volume, while the heart rate remains ordinarily within normal limits during the period of recovery.

Simultaneously, the total circulatory volume was found reduced^{169, 202} and the venous pressure

exists in a normal situation immediately following the establishment of myocardial necrosis cannot be classified as congestive failure. Peripheral resistance may remain relatively high and suggests the

ocardial infarction are seen during lifetime without any corresponding morphological findings being obtainable at autopsy³⁸². Such electrocardiographic alterations may appear temporarily in attacks and disappear completely during the intervals³⁸³.

The designation "*acute coronary insufficiency*" has been proposed for episodes of severe necrotizing myocardial anoxia without coronary occlusion^{420 1571}, in keeping with the customary emphasis on the alleged primacy of coronary narrowing in almost all forms of myocardial oxygen deficiency. While this term is not objectionable in itself, it entails the disadvantage of tending to divert attention from the chemical anoxia-producing factors involved and thus to perpetuate strictly non-chemical thinking among cardiologists. Here, as in cases of only conjectural "coronary occlusion", the non-prejudicial diagnostic term "*anoxic myocardial necrosis*" would seem preferable.

A clinical differentiation between anoxic myocardial necrosis, caused merely by paroxysmal adrenal medullary or sympathetic neurosecretory discharges on one hand, and by coronary occlusion on the other, is often not possible. However, absence of all indications of acute sympathetic stimulation before onset, the presence of electrocardiographic signs of a circumscribed lesion and a pericardial friction rub will strongly favor the diagnosis of the much more common event of a true coronary occlusion and infarction.

An apparent connection between the occurrence of cardiac accidents and meteorological conditions has been ascribed to influences of the latter upon the vegetative nervous system³²²³. It seems quite probable that the reported maximal incidence of myocardial anoxic episodes during the winter months^{183, 186 2232, 2297, 2566, 2677} is also based on some hormonal and neuro-hormonal mechanisms, but their nature has not yet been clarified. The same is to be said concerning the possible contributory role of occupations and living habits^{118 143 2217 2232 2746}. The observation that myocardial accidents occur with greater frequency among individuals engaged in physically less arduous occupations than others³⁶⁹¹, appears compatible with the hypothesis that habitual, reasonably vigorous physical work tends to train the oxygen-sparing cardiac vagal tonus as a counterbalance against sympathogenic oxygen wastage (p. 11 ff., Fig. 49, p. 374).

Whether or not *tobacco smoking*, by virtue of its sympathetic stimulating effect, serves as a predisposing factor in the development of anoxic myocardial necrosis has not been definitely decided; but a report according to which 94 per cent of a series of 151 male cases of coronary thrombosis (average age 52 years) had been smokers, with the average age of the heavy smokers being 47 years and that of the non-smokers 59½ years²¹²⁵, appears significant.

The widespread but probably unfounded fear of vagal coronary constriction prompted the use of atropine in the treatment of acute myocardial anoxia¹⁷⁴⁴. However, neither clinical experience^{1069, 1995} nor more recent experimental observations²³⁰ lend convincing support to the earlier belief that atropine exerts a significantly beneficial action in the presence of coronary occlusion^{1574, 2131}. On the contrary, its cardio-acceleratory effect and reduction of the desirable oxygen-sparing vagal influence upon myocardial metabolism^{1799a} would rather seem to make it quite unsuited

In the case of an only moderate fall of blood pressure, no special therapeutic measures are necessary, as this reflex phenomenon is indeed being considered an advantageous one^{2092, 2093}. However, if outright shock develops with an abrupt pressure fall to 90 mm or below, a rapid small pulse and cold moist skin, and in the absence of pulmonary congestion, the application of pressor drugs is indicated. Epinephrine should not be given because of its detrimental effects on myocardial metabolism and its peripheral vasoconstrictor action. Nor-epinephrine, on the other hand, is a generally vasoconstrictor agent and elicits sufficient reflexory vagal counter-effects on the heart to prevent an aggravation of myocardial hypoxia. Clinical trials with the sympathomimetic amines mephentermine and ephedrine^{231, 1132} yielded likewise encouraging results. Five to 15 mg of the latter were given intravenously as an initial dose, followed, if necessary, by 35 to 70 mg in 100 ml water with 5 per cent glucose, infused over two hours and with frequent controls of blood pressure, pulse and electrocardiogram. Instead of the intravenous infusion, 25 mg can be administered intramuscularly every one to two hours. The blood pressure should be maintained at a level near 100 mm. If this is not feasible and if there are no signs of congestive failure, small amounts of plasma (maximum 250 cc) may be infused over one hour or more ^{only}¹⁴⁵²

Supervening pulmonary edema requires immediate drastic action. Apart from the inhalation of oxygen which must always be kept in readiness in critical cases, morphine should be administered in sufficient dosage, unless contraindicated because of emphysema. Its vagotropic mode of action is of great value in pulmonary edema (p. 506). Atropine is is

or particularly in patients with pre-existing heart disease, venipuncture with removal of up to $\frac{1}{2}$ liter of blood is to be considered during attacks of marked pulmonary edema

Unless the patient has received digitalis within about two weeks pre-

*persistence of a peripheral sympathicotonic component beside the vagal influences upon cardiac action*³⁰⁰¹. Coronary ligation in animals was found to reduce the cardiac output 50%, probably due to inhibition of venous return and of sympathetic action upon the heart³⁰⁰².

Apparently no systematic studies have yet been devoted to the functional state of the adrenal cortex in connection with shock resulting from necrotizing myocardial anoxia, and to its role in the process of recovery. It seems likely that significant alterations of cortical function must be induced by such violent upheavals in the neurovegetative system and hemodynamic equilibrium.

Treatment

It is not intended to give here a complete outline of the management of acute anoxic myocardial accidents and of their aftermaths, nor to discuss the merits of the "chair treatment"¹⁹⁹¹ *vs.* prolonged bed rest, of the anticoagulants, etc. Instead, an attempt will be made to evaluate some of the customary forms of treatment from the point of view of their influence upon the neurohormonal and cardiac metabolic factors which participate in the pathogenesis of the syndrome of anoxic myocardial necrosis

Since the main concern in an acute attack is the *suppression of pain*, nitroglycerine is often used before anything else but with a characteristic lack of efficiency which serves in itself as a diagnostic criterion, especially in patients who had found nitrites promptly helpful in previous attacks of angina pectoris. The reason for the non-effectiveness of nitroglycerine in cases of coronary occlusion is obviously the uselessness of its vasodilator properties under such circumstances, but probably also the impossibility of its access to the ischemic areas of the myocardium where it might otherwise help to correct those hypoxic metabolic changes which cause pain (p. 405 ff)

The mode of action of morphine, the classic and still unequalled, although not uniformly effective, remedy for the relief of the crushing pain of coronary occlusion, is likewise more complex than usually realized. Apart from its central pain-soothing effect, it possesses definite vagotropic properties¹¹⁵⁴, and thus may contribute to the vagal mechanisms which keep myocardial dynamic activity and oxygen requirements within limits. Doses of less than 17 mg ($\frac{1}{4}$ gr.) are rarely worth-while, but, on the other hand, morphine should be avoided entirely if pain and restlessness are not severe, if existing emphysema threatens to cause respiratory difficulties and if deep shock prevails. In such cases, it may be replaced by dilaudid or demerol in cautious dosage and under close supervision of respiration, blood pressure and heart rhythm.

relatively high percentage of myocardial "infarctions". In the majority of these latter instances, the heart displayed some degree of coronary arterial narrowing and/or ventricular hypertrophy.

Strenuous exercise, emotions, tachycardia and similar conditions, which are associated with excessive adrenergic neuro-secretion, could be identified as precipitating factors in most cases of myocardial necrosis without coronary occlusion. This fact, in conjunction with the experimental production of myocardial necroses in otherwise normal hearts by enforced exercise, electric stimulation and injection of epinephrine, suggests that the necrotizing lesions are due to the well-known hypoxia-producing chemical effect of acute excessive catecholamine discharges, especially in hearts whose oxygen supply had been more or less reduced from the beginning.

Since a definite clinical differentiation between "infarction" and non-occlusive necrotizing myocardial anoxic accidents is often not feasible, the non-prejudicial term "anoxic myocardial necrosis" seems to be appropriate for both eventualities.

In some of those numerous cases in which an occluding intramural hemorrhage in a sclerotic plaque of a coronary branch occurs in apparent connection with a sympathicotonic situation (exertion, emotion, surgical operation, etc.), the local mechanical effect of abrupt sympathogenic coronary dilatation may be considered as a possible immediate cause of intramural capillary rupture.

In the development of early "neurogenic" shock following an anoxic myocardial accident, a preponderance of the peripheral vasodilating action of circulating epinephrine, unaccompanied by the otherwise prevailing increase of cardiac output, can be suspected as being prominently

responsible (see also the preceding effect), originating in the chemically damaged ventricular musculature itself. This mechanism is probably also responsible for prolonged reductions of blood pressure. The usually low venous pressure indicates that congestive heart failure is not a regular constituent of the syndrome of anoxic myocardial necrosis.

Rest is an efficient therapeutic measure by reducing sympathogenic chemical and dynamic influences upon the heart muscle. The vagotropic action of morphine and the oxygen-sparing effect of strophanthine prove useful, if judiciously applied in appropriate situations, such as cardiac pain and impending or developed pulmonary edema and congestive cardiac failure. Nor-epinephrine may prove beneficial in the treatment of early neurogenic shock following anoxic myocardial accidents. Epinephrine and atropine are contraindicated.

viously, strophanthine (0.2 mg 1-3 times within 24 hours, injected slowly into a vein) is to be recommended as rapidly acting emergency medication for critical pulmonary edema because of its almost immediate effect on cardiac dynamics and myocardial oxygen utilization¹²⁶⁷.

Routine digitalization is not only unnecessary, as a rule, but indeed, is frowned upon by many clinicians because of the hazard of possibly precipitating cardiac rupture and of contributing to the mobilization of mural thrombi through the increased vigor of ventricular contractions. Nevertheless, these potential dangers must be accepted if outright cardiac failure with severe dyspnea, cyanosis and peripheral edema sets in.

Xanthine drugs (aminophylline and others), injected or in the form of rectal suppositories, are especially useful for the prevention of nocturnal dyspnea and Cheyne-Stokes respiration.

Physical and mental rest, the division of the daily food intake into six or seven small meals, and the avoidance of gas-forming foodstuffs are intended to protect the damaged heart from any direct or reflectory sympathetic stimulations which might impose an unnecessary mechanical and metabolic strain upon the myocardium. This applies also to tobacco smoking, at least during the period of convalescence. Constipation should be prevented through an appropriate diet and mild laxatives if necessary.

The transient *hyperglycemia and glycosuria*, which occur not infrequently during the first days following an anoxic myocardial accident, do not require special treatment, but diabetic patients must be carefully watched as they are apt to sustain a marked reduction of their carbohydrate tolerance and to slip into coma. Insulin must be administered in doses sufficient to keep the diabetic situation under control, however with a certain safety margin of the dosage which must be worked out meticulously so as to circumvent any possibility of hypoglycemia even if a moderate glycosuria and elevation of the blood sugar level persist. The danger of hypoglycemia rests largely in secondary discharges of epinephrine and their disastrous influence on myocardial oxygen economy (p 11 ff.). To avoid them, it is advisable to apply individually adjusted doses of insulin before meals rather than any of the depot insulin preparations.

A supposedly beneficial effect of testosterone upon the healing of coronary infarctions could not be confirmed in experiments with artificial coronary occlusion in dogs²³⁴³

Summary

(Not all episodes of necrotizing myocardial anoxia are ascribable to an actual occlusion of the supplying vessels which lead to the respective damaged area. In fact, *complete occlusions were found to be absent in a*

occurrences from the Philippine Islands where this form of death is popularly known by the term "bangugut", indicating nightmares. No precipitating causes could be identified. Women are not affected. In Honolulu County alone, 81 cases were registered between 1937 and 1948²²².

Sudden death is a comparatively common event in patients with pheochromocytoma and other types of adrenal pathology (p. 85 ff., 430).

Sudden cardiac standstill with potentially fatal outcome, unless instantaneously treated, is seen in individuals with normal hearts as an occasional complication of anesthesia for surgical procedures.

Little is known of the subjective sensations connected with the seizures which lead rapidly to death. In more than half of the cases, syncope or convulsions²²³ preclude communication with the dying person; others complain of headaches, substernal or epigastric pain²²⁴.²²⁵ Groaning, gasping, coughing and choking were frequently observed preceding the Filipino deaths.

Pathology

The extensive report by Moritz and Zamcheck²²⁶ on sudden deaths of young soldiers contains a group of at least 140 carefully investigated sudden deaths in which the post-mortem findings were essentially normal. Complete pathological examination, supplemented in many instances by toxicologic studies, failed to disclose the cause of death. It was estimated that such cases represent more than 10 per cent of all sudden non-traumatic deaths of apparently healthy young men. Apart from such unequivocally negative autopsy reports, there are many which include certain abnormalities, the significance of which for the occurrence of death remains open to question. Among the young Filipinos mentioned above, however,

complete occlusion" in many autopsies, however with "no site of complete occlusion" in other instances²²⁷.

Coronary sclerosis (with or without occlusions and thromboses) was 67.7 per cent and 63.3 per cent respectively in two large series of cases of sudden cardiovascular deaths, compiled in New York City²²⁸ and in Berlin²²⁹.

Many pathologists seem to take it for granted that the presence of coronary sclerotic lesions of a major degree, or of any degree, if unaccompanied by other significant findings, suffices to regard coronary arteriosclerosis per se as the cause of death. Only few attempts were made so far to explain the obvious incongruity of static vascular lesions with the dramatic acuteness of supervening death, especially in the absence of exertion, emotion or other identifiable precipitating functional causes. The by no

Cardiac Death Without Morphological Substrate; Disturbances of Ventricular Rhythm

Definition and General Principles

In various published series of sudden, unexpected deaths, there is a considerable number of instances in which autopsy revealed either no significant morphological findings at all or minor anatomical changes which can be considered as causes of death only by a wide stretch of the imagination.

The majority of cases of sudden, unexpected death (excluding violence, trauma and poisoning) is attributable in one way or another to a primary cardiac disturbance, consisting either of ventricular fibrillation or of cardiac standstill²³⁰⁵. A diagnostic differentiation between these two alternatives is only rarely possible for obvious reasons. More than one-third of the cardiac deaths reported in one series occurred in bed, unnoticed by others²⁷⁷. Of those observed by witnesses, about 60-80 per cent occurred instantly or within a few minutes after onset of the fatal seizure^{2379 2727}. Complete cardiac standstill of more than eight minutes is generally considered as absolutely fatal, but there are exceptions to this rule and recovery after 20 minutes of cardiac arrest has been reported¹⁰.

In the great majority of 140 young soldiers who died suddenly without presenting any explanatory post-mortem findings, no definite relation between the types of activity at the time of the fatal seizures and the latter could be established²²⁷⁹. Twenty-four per cent died during sleep, 23 per cent during strenuous exercise. In other smaller groups of cases or in individually published instances, however, emphasis was placed by the respective observers on a coincidence between preceding exertion^{271 261 1035 1664 1665 1731, 2200 2224 3576} or emotions^{40 343 2001, 2224 2230 2254} and death.

Existing statistics of sudden cardiac deaths do not yield any conclusive information regarding the role of age, sex and race in the subgroup which was found free of significant morphological changes^{1035 2279 2514}. No age category seems to be exempt, as such incidents have also been observed in children³⁵⁷⁶.

A disproportionately high occurrence of unexpected and unexplained deaths of young, seemingly healthy male Filipinos during sleep was reported by the coroner of Honolulu County²¹⁹³ who also obtained data on similar

ably after injection of epinephrine whenever the myocardial concentration of catecholamines transgressed a rather sharply defined critical maximum (17-20 gamma equivalents per gram of heart muscle). Since death from epinephrine can be markedly delayed or prevented in the rat by artificial respiration of oxygen²¹²⁶, it would appear that ordinarily a summation of two types of anoxia in the heart muscle contributes to the ultimate fatal outcome, namely one caused by local excessive oxygen consumption, and the other caused by impaired function of the respiratory center which in turn would lead to inadequate oxygenation of the blood that reaches the heart. The high fatality of a combination of otherwise non-lethal doses of epinephrine and of otherwise non-lethal reductions of atmospheric pressure²¹²⁶, appears to support this view. Conditions in the human may be different, however, insofar as the human heart is very much more sensitive to epinephrine than that of the rat, so that ventricular fibrillation and cardiac death might be expected to result from relatively small amounts of epinephrine (or of sympathogenic, locally discharged catecholamines) directly. Excessively high concentrations of catecholamines were found by the writer^{2174, 2177} in the hearts of two young, essentially healthy persons who succumbed to a sudden unexpected death without previous history of heart disease. The coronary arteries and the myocardium were macroscopically and microscopically normal in both cases and there were no significant morphological autopsy findings, except for some pulmonary congestion, and thyroiditis in one of the two (Fig. 70). In a third case of sudden, unexpected cardiac death in which a fresh coronary thrombosis and adrenal cortical adenomas were found, the myocardial catecholamine concentration was likewise excessively high (Fig. 70).

(Observations like those above enumerated make it appear likely that sudden death in healthy individuals is induced by the influx of excess amounts of adrenosympathogenic catecholamines into the myocardial cells and that this is a toxic process.)

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the adrenal medulla or from the sympathetic nervous system. Epinephrine or nor-epinephrine, either from

interplay of neurogenic and enzymatic reactions rather than by the inert state of coronary sclerosis per se, unless the latter has formed the pathogenic background for a sudden vascular occlusion. Again, the yet unanswered

means uncommon long survival of persons suffering from very much more marked coronary sclerosis, with or without myocardial infarctions, casts further doubt on the significance of slight or moderate coronary sclerotic changes as the ultimate cause of death.

In some cases of sudden and unexplained death, the cardiac lesions found were limited to *disseminated foci of myocardial degeneration*^{1271, 1457, 2051, 2221, 2421}, similar to those produced in normal hearts by fatal or non-fatal epinephrine injections, strenuous exercise and other forms of intense sympathetic stimulation (p. 18 ff.).

Pulmonary congestion was observed in 49 per cent of 140 cases of "obscure" sudden death²⁵⁷⁹ and in 69 per cent of 450 cases of sudden death supposedly due to coronary sclerosis³⁶⁹¹. Congestion of liver and kidneys was likewise frequently observed.

Among cardiac lesions other than arteriosclerotic which are found in cases of sudden death, aortic stenosis and syphilitic aortic insufficiency are relatively common¹⁰⁶⁰.

Neurohormonal and Hormonal Aspects

Sudden death, i.e., death within minutes, occurs in animals with great regularity if epinephrine is injected in large doses^{2670, 2678, 2700}. In humans, rapid death has been induced inadvertently by the administration of overdoses of epinephrine in several instances, none of which seems to have been published, however⁹⁹³. Ventricular ectopic pre-fibrillation rhythms, which are believed frequently to precede sudden cardiac death^{1993, 2421, 3541}, were recorded in humans after injection of epinephrine²⁴²¹. Pre-treatment with thyroid hormone greatly increases the susceptibility to a rapidly fatal effect of injected epinephrine^{1749, 2533a, 2673}.

Sudden, unexpected death was frequently observed in patients with various types of adrenal pathology, especially in cases of pheochromocytoma^{769, 1557, 2342, 2542, 3111, 3603}, also in connection with cystic degeneration and hemorrhages^{649, 1462, 1555, 3095, 3149}, infection^{2217, 3149}, tumor metastases³¹¹⁹, round cell infiltration and edema²⁶¹ of the adrenals.

A substantial fraction of all cases of sudden death supervened in more or less close connection with physical exertion and emotional excitement, thus under circumstances which are associated with adrenal medullary and sympathetic neurosecretory discharges of catecholamines which cause chemical hypoxia or anoxia of the heart muscle, especially in the presence of diminished coronary arterial dilatability. A classical example seems to be the famous Marathon runner who collapsed dead after having reached Athens and after having shouted the news of the victory over the Persians in 490 B.C.

Sudden death in rats was found by the writer^{2670, 2678, 2700} to occur invari-

ably after injection of epinephrine whenever the myocardial concentration of catecholamines transgressed a rather sharply defined critical maximum (1.7-2.0 gamma equivalents per gram of heart muscle). Since death from epinephrine can be markedly delayed or prevented in the rat by artificial respiration of oxygen²⁰⁶, it would appear that ordinarily a summation of two types of anoxia in the heart muscle contributes to the ultimate fatal outcome, namely one caused by local excessive oxygen consumption, and the other caused by impaired function of the respiratory center which in turn would lead to inadequate oxygenation of the blood that reaches the heart. The high fatality of a combination of otherwise non-lethal doses of epinephrine and of otherwise non-lethal reductions of atmospheric pressure²⁰⁰, appears to support this view. Conditions in the human may be different, however, insofar as the human heart is very much more sensitive to epinephrine than that of the rat, so that ventricular fibrillation and cardiac death might be expected to result from relatively small amounts of epinephrine (or of sympathogenic, locally discharged catecholamines) directly. Excessively high concentrations of catecholamines were found by the writer²⁷⁴⁻²⁸⁷ in the hearts of two young, essentially healthy persons who succumbed to a sudden unexpected death without previous history of heart disease. The coronary arteries and the myocardium were macroscopically and microscopically normal in both cases and there were no significant morphological autopsy findings, except for some pulmonary congestion, and thyroiditis in one of the two (Fig. 70). In a third case of sudden, unexpected cardiac death in which a fresh coronary thrombosis and adrenal cortical adenomas were found, the myocardial catecholamine concentration was likewise excessively high (Fig. 70).

Observations like those above enumerated make it

particularly vulnerable and excitable "trigger zones" of the myocardium which are believed to initiate the onset of fatal ventricular fibrillation¹⁹². It seems readily imaginable that persons with pre-existing coronary sclerosis and a reduced coronary dilatability will be especially susceptible to locally hypoxiating harmful effects of epinephrine or nor-epinephrine, either from the adrenal medulla or from the sympathetic

interplay of neurogenic and enzymatic reactions rather than by the inert state of coronary sclerosis per se, unless the latter has formed the pathogenic background for a sudden vascular occlusion. Again, the yet unanswered

question of adrenergic-cholinergic and cellular enzymatic balance suggests itself as the possible key to an understanding of the wide range of cardiovascular sensitivities to the chemical action of the catecholamines. A minute dose may suffice to kill one individual instantaneously, while another may tolerate enormous quantities without any significant disturbance¹⁵⁷. In an occasional instance, ventricular tachycardia of the catecholamine-induced pattern sets in quite abruptly and without any premonition, in persons apparently free from "organic" heart disease^{154, 204, 244, 353}, and may sub-

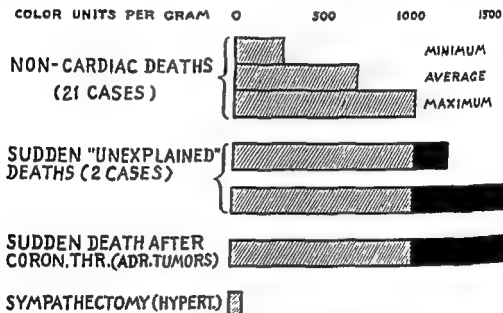


FIG 70 Catecholamine concentrations in human hearts
(After W Raab, Ann Int Med 28 1010, 1945)

side again at the very threshold of impending death after having caused chest pain, dyspnea and pulmonary edema²⁵⁶.

A well-known example of artificial conditioning of the myocardium for epinephrine- (and intrinsic sympathogenic nor-epinephrine-?) induced ventricular fibrillation, is the effect of cyclopropane anesthesia^{232 233} on the heart. Thyrotoxicosis has also been suspected as predisposing to fatalities during surgical interventions^{353a}.

The post-mortem finding of clinically unrecognized heart disease, arteriosclerotic or other, in the great majority of persons who had displayed ventricular tachycardia before death²⁶⁰ emphasizes the importance of established cardiac lesions as an eminently predisposing cause of sudden death. It also stigmatizes the victim posthumously as one who had been presumably exposed to many cardiotoxic catecholamine discharges during his lifetime. The relatively narrow margin between physiological and lethal

catecholamine concentrations in the heart muscle of animals as well as humans^{267, 268, 270}, suggests that every one of us lives constantly much closer to potential "physiological" cardiac death than we realize.

The second alternative of cessation of cardiac function: cardiac arrest as a result of cholinergic vagal preponderance^{223, 232}, is generally attributed to the interference of vasovagal and vagovagal reflexes, as in the cases of the carotid sinus syndrome (p. 334 ff.), gastric distention^{211, 212, 213, 214, 215, 216}, tracheal intubation¹⁸ and various other manipulations on intrathoracic organs¹⁶. Interestingly, the type of reaction of both the heart rate and the electrocardiographic ventricular complexes to artificial inflation of the stomach proved to depend on the existence of either sympathicotonic or vagotonic prevalence in the subjects examined¹⁷⁴. In the former, it produced tachycardia, increase of the pulse pressure, depression of the T-wave and sometimes anginal pain, in the latter, cardiac retardation, diminution of the pulse pressure, elevation of T and never anginal symptoms. Elimination of vagal preponderance through atropine transformed the reaction pattern of the vagotonic individuals into one identical with that seen in sympathicotonic subjects¹⁷⁴. On the other hand, a back and forth swaying of the delicate balance between cholinergic and adrenergic supremacy may manifest itself by alternating periods of ventricular tachycardia and standstill

... one may over-estimation of the pathogenic significance of coronary vascular responses to neurovegetative stimuli. The influence of coronary circulatory changes upon myocardial oxygen economy is largely, or entirely, outweighed by the direct chemical effects of adrenergic and cholinergic action respectively upon cardiac oxygen consumption (p. 374). Hence, the problem of sudden "physiologic" death must be considered primarily as one of direct neurohormonal chemical interference in myocardial metabolism and only secondarily, if at all, as one of coronary circulatory alterations.

Preventive and Therapeutic Measures

Obviously, a discussion of measures for the prevention of sudden death in apparently healthy persons would have to be

... of repeatedly occurring recognized attacks of ventricular tachycardia, each of which must be regarded as involving the danger of instantaneous death, quinidine (0.2 gram every 4-6 hours) was found valuable for preventive management during the interval^{130, 222, 223} but should not

be given in the presence of auriculoventricular block²⁹⁵². During the attack, an antagonistic stimulation of the vagus should be attempted by unilateral digital pressure on the carotid sinus, which the patient may learn to perform himself. Deep inspiration, breath-holding, the Valsalva experiment, pressure on the eye bulbs, provocation of the pharyngeal retching reflex, etc., are other primitive emergency manipulations which may or may not terminate the attack. If these attempts fail, quinidine sulphate (0.2 to 0.3 gram or more) can be given every two hours orally or in a single, very slow intravenous injection (up to 0.5 grams), unless idiosyncrasy exists. In the latter case, digitalization or, in non-digitalized patients, strophanthin (0.2 to 0.3 mg intravenously) or any of the crystalline digitalis glycosides may be administered two to three times per day until cessation of the tachycardia. Mecholy¹²³⁵ (30-40 mg subcutaneously), prostigmine⁴⁶² (0.5-1.0 mg subcutaneously) and magnesium sulphate (15-20 cc of a 20 per cent solution slowly injected intravenously; contraindicated in cases of myocardial lesion)²⁵⁶ have also been found useful in numerous instances. Probably the most effective drug for both termination and prevention of ventricular tachycardias is pronestyl (procaine amide). During the attack it has to be administered intravenously at a slow rate (25 to maximally 100 mg per minute until a normal rhythm is restored or until a total of 1.0 gram has been infused). The blood pressure must be frequently measured because of the accompanying hypotensive effect which may even necessitate interruption of the infusion. It may be checked in critical cases by intravenous neosynephrine³²⁵¹. Preventive oral medication with pronestyl (maintenance dose 0.5 to 1.0 g every three to six hours) does not produce hypotension and may be continued over months¹⁷²³.

In the case of frequent episodes of recognized ventricular standstill, which are caused by auriculoventricular block and comparatively harmless, ephedrine (30-60 mg every eight hours), epinephrine intramuscularly^{2950, 2954}, epinephrine in oil or aminophylline (0.5 gram suppositories) twice or three times per day²⁹⁵⁷, are recommended for prevention. During the attack, pounding of the cardiac area and intracardiac injection of caffeine sodium benzoate²⁹⁵⁷ have been used with good results. Intracardiac epinephrine may precipitate ventricular fibrillation.

It is important that prophylactic measures be instituted only after the nature of the attacks to be prevented has been identified with reasonable certainty, preferably by means of electrocardiographic study during attacks, since undesirable effects, opposite to those intended, may result if the therapeutic indication was made incorrectly.

Cardiac arrest during surgical intervention can be combated successfully by artificial oxygen respiration plus massage of the heart and, if available, by insertion of an electrical "artificial pacemaker" into the right auricle¹⁶⁷².

In the case of ventricular fibrillation, electrical shock must be applied at once if possible and supplemented by procaine. Epinephrine in small doses has been advocated as an adjuvant after the administration of procaine¹¹⁴. Technical details are described in various publications^{100a, 101a, 101b, 101c}.

Summary

Sudden, unexpected cardiac death from ventricular fibrillation or standstill has been observed in a sizable number of cases without any morphological abnormality of the heart and coronary arteries and in other seemingly healthy individuals in whom autopsy revealed various degrees of coronary sclerosis but no myocardial lesions. The morphological findings obtained in such cases are usually insufficient by themselves to explain the occurrence of sudden death.

In a number of cases, rapid fatalities have been precipitated by *over-doses* of epinephrine, sudden death supervenes relatively frequently in patients harboring pheochromocytomas, sometimes it occurs under circumstances conducive to adrenergic sympathetic catecholamine discharges (exertion, emotional excitement); the margin between physiological and lethal myocardial catecholamine concentration is narrow, at the autopsy of two young persons who had died suddenly and unexpectedly, no abnormalities were found except an excessive concentration of catecholamines in the heart muscle. These observations make it appear likely that sudden death may be precipitated in many instances by abnormal adrenergic discharges, especially if these lead to an adrenergic-cholinergic imbalance in certain excitable trigger zones of the heart muscle, resulting in ventricular fibrillation. Coronary sclerosis acts often as a predisposing factor.

Death from vagovagal and vagovagal reflexory cardiac arrest seems to be less common. The importance of coronary constriction for the mechanism of sudden death has probably been grossly over-estimated.

Therapeutic measures to prevent recurrences of attacks of ventricular tachycardia or standstill should not be applied unless it is

Beri-beri Heart Disease

A discussion of the so-called "beri-beri heart" is being included in the present review because some of its clinical and pathological features, as well as experimental observations, are strongly suggestive of a decisive involvement of neurohormones in its pathogenesis.

Definition and General Principles

Since the first systematic description of the cardiac phenomena, pertaining to the syndrome of "wet" Oriental beri-beri, by Aalsmeer and Wenckebach in Java in 1929², and of similar syndromes, occurring in the Western hemisphere, by Weiss and Wilkins in Boston in 1936³⁴⁷, an extensive literature on the subject of the effect of thiamine deficiency on the heart and circulation has developed. It became gradually evident that despite striking but not quite regular similarities in some details, the cardiovascular symptomatologies of Oriental and Occidental beri-beri differ to such an extent that certain fundamental differences, also in the pathogenic background, must be assumed. This was especially stressed by Aalsmeer¹ and by Blankenhorn²⁹⁰ with emphasis on a primary, comparatively pure deficiency of thiamine intake in the Oriental form, as contrasted with the prominent role played by alcoholism in the Occidental cases. In the latter, a combination with other nutritional deficiencies and possibly with different pre-existing subclinical cardiovascular lesions seems to contribute to the peculiarities which distinguish the Occidental beri-beri heart disease from its Oriental counterpart and which cause a much greater resemblance to other more common forms of congestive failure. In a large urban hospital material, the occurrence of Occidental beri-beri heart was calculated as amounting to 0.1 per cent²⁹⁰. The syndrome observed in South America (Brazil)⁴⁴⁹ seems to be of a similar pattern, while the South African cases³²⁴ occupy an intermediate position between the Oriental and the Occidental extremes (see below).

It is not exactly known in which way a lack of thiamine interferes in cardiovascular tissue metabolism and function. Some experimental observations indicate that the thiamine-deficient heart muscle does not take up and does not metabolize pyruvate from the blood but rather pours out locally formed pyruvate into the circulation²⁷³. This behavior was explained with reference to the fact that thiamine is necessary for the utilization of carbohydrates since it acts as cocarboxylase in the oxidation of the carbohydrate

split product pyruvate acid. Consequently, the myocardial carbohydrate metabolism seems to be deranged in thiamine deficiency.

Symptomatology

Apart from general and neurological manifestations, such as fatigue, weakness, mental depression, irritability, insomnia, dizziness, anorexia, nausea, paresthesias of the legs, paresis, etc., the symptomatology of the *Indonesian and South African form of beri-beri* includes some characteristic cardiovascular phenomena which are dominated by signs of a greatly decreased peripheral vascular resistance ("shunt circulation") in combination with marked cardiac stimulation: a low diastolic pressure and large pulse pressure ("water hammer pulse") with a normal mean pressure, "pistol shot" sounds over the arteries, tachycardia, palpitations, irregularities of cardiac rhythm, substernal pain, especially on exertion, and dilatation of the heart^{1 224 241}. Excretion of ingested NaCl and of water is delayed^{1 224}. Intake of extra salt precipitates the formation of edema, without a significant change of blood chloride concentration²²⁴. Nevertheless, cardiac decompensation and definite electrocardiographic changes fail to appear until the last, premortal stage, when the fully developed cardiac picture with prevalence of right ventricular failure ("sho-hin") sets in more or less acutely^{2 224}. Shock and syncope are frequently observed events.

Although some of the Occidental cases present a similar hemodynamic pattern^{161 250 257}, there are many among them and also among those occurring in China¹⁷⁷ in which an accelerated circulation and diminished peripheral resistance are not demonstrable. They rather resemble the more common forms of degenerative heart disease in that they develop besides

comparative rarity of electrocardiographic changes in Oriental beri-beri¹, a variety of abnormalities was observed in the North and South American and South African cases, such as flat or inverted T-waves, depressed S-T, prolongation of Q-T, low voltage, occasional extrasystoles and auricular fibrillation^{220 440 521 541 249 2513}. A slow heart rate is sometimes seen^{224 2637} but it turns into tachycardia during exertion²²⁴.

Electrocardiogram -

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United States may be found as a complication of other forms of heart disease, particularly since nutrition is often inadequate in cardiac patients³⁵⁰. She suggests the following criteria for differential diagnosis: "(1) enlargement of the heart with normal (sino-auricular) rhythm, (2) dependent edema; (3) elevated venous pressure; (4) peripheral neuritis or pellagra; (5) non-specific changes in the electrocardiogram; (6) no other cause evident; (7) gross deficiency of diet for three months or more; (8) improvement and reduction of heart size after specific treatment or autopsy findings consistent with beri-beri".

Pathology

Dilatation of the right heart and an edematous swelling of the myocardium were described as characteristics of Oriental beri-beri³⁴¹. However, in Occidental cases, the right ventricular enlargement may be lacking³⁴⁹, some show general hypertrophy or only dilatation^{350, 351}. Interstitial edema, degenerative and necrotic myocardial lesions of unspecific appearance are common though not constant findings^{350, 341}. In experimental thiamine deficiency, they are observed with considerable regularity^{79, 1015, 2032, 2129, 3330, 3371, 3442}.

Neurohormonal and Hormonal Aspects

The hemodynamic characteristics of the classical Oriental beri-beri syndrome (peripheral vasodilatation, increased pulse pressure, heart rate and stroke volume), the elevation of the basal metabolism^{1419, 2471}, the occasional anginal symptoms³³²⁴, the electrocardiographic findings (depressed S-T and T) and the histological lesions of the myocardium (edema, necrotic foci) are highly suggestive of an exaggerated activity of epinephrine, since all of these phenomena can be induced by the injection of epinephrine (p. 9, 18). This impression is further strengthened by the observation of the writer and Supplee²⁷²⁰, recently confirmed by Goodall^{1206a}, that the heart muscle of thiamine-deficient animals contains abnormally large amounts of catecholamines (epinephrine and nor-epinephrine) which return promptly to normal after administration of thiamine²⁷²⁰ (Fig. 71). Moreover, abnormally high epinephrine levels were found in the blood of thiamine-deficient animals²⁹¹⁶ and a diminished epinephrine concentration in the adrenal medulla^{1206a}. In mild clinical cases and in convalescents, the typical severe "shoshun" syndrome can be precipitated by the injection of epinephrine²¹¹⁹ and the hemodynamic manifestations of beri-beri are readily called forth both by epinephrine and by exercise¹. An increased epinephrine sensitivity was observed also in Occidental cases of beri-beri heart disease³³⁴⁰.

This latter phenomenon is of interest because it constitutes one of several features which beri-beri heart disease has in common with the thyrotoxic

heart and with the hemodynamic situation in thyrotoxicosis. It will be recalled that an exaggerated activity of epinephrine under the potentiating influence of the thyroid hormone was considered the fundamental derangement underlying the cardiovascular manifestations of thyrotoxicosis (p. 144 ff.). On the other hand, there are indications that a certain degree of functional thiamine deficiency is involved in the thyrotoxic syndrome¹⁹¹.¹⁹⁵ ¹⁹⁶ ²⁰⁰ and some workers have gone so far as to interpret the congestive failure occurring in advanced "thyro-cardiacs" as a possible result of co-existing vitamin B₁ deficiency²⁰⁰, ²⁰⁶.

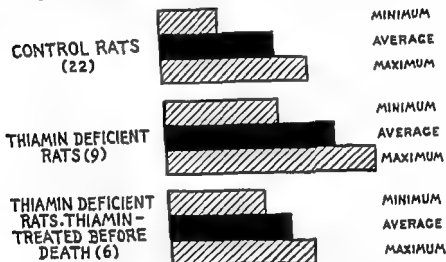


FIG 71 Effect of thiamine deficiency and of thiamine-treated thiamine deficiency upon myocardial catecholamine concentration in the rat (See also^{199a}).
(After W. Raab and G. C. Supplee, Exp Med and Surg 2: 152, 1944)

Be that as it may, there can be little doubt that the cardiovascular changes of both beri-beri and thyrotoxicosis are largely determined by excessive epinephrine action both on the heart and the vascular system. It must be emphasized, however, that not all cardiac manifestations, induced by thiamine deficiency, can be explained simply on the basis of epinephrine preponderance and its sympathomimetic implications. In fact, there are some phenomena which point toward an at least temporarily prevailing vagal cholinergic activity. bradycardia has been noted occasionally in clinical cases at rest¹²², ²⁵⁰ and more frequently in thiamine-deficient animals¹²¹, ²⁷⁴, ⁴⁹², ⁷⁹⁵, ²⁵²³, ²³³⁰, ²⁶⁵⁵, but the stage of cardiac failure is usually heralded and accompanied by cardiac acceleration²⁵¹. Occasional elevations of the T-wave, prolongations of the P-R interval and atriculo-ventricular block²⁵⁴, ²⁶⁵⁵, ²⁷¹² are probably likewise of vagal origin. The occurrence of

auricular fibrillation³⁶⁵ suggests a collision between increased adrenergic and cholinergic action, as it is also assumed to exist in thyrotoxicosis (p. 133). The thiamine-deficiency-induced bradycardia in animals could be abolished by vagal section or atropine^{49, 365}. This observation and the finding of an about 10-fold increase of acetylcholine in the heart muscles of thiamine-deficient animals²³² lend support to the concept that thiamine deficiency leads to an exaggeration of vagal cholinergic activity as well as to increased adrenergic neurosecretion. Acetylcholine does not only exert "muscarinic" vagal effects but it stimulates also the liberation of epinephrine in the heart muscle³⁵¹. It seems possible, therefore, that the adrenergic manifestations of beri-beri heart disease may be provoked by a primary overproduction or deficient inactivation of acetylcholine.

Morphological studies of the central and peripheral nervous system, especially of the nucleus sympathicus and the tracts of the lateral horn in the upper cervical segments, the spinal cord roots, the sympathetic chains and the vagi, revealed degenerative lesions^{290, 367} which lead Wright³⁶⁷ to the conclusion "that almost the entire cardiac nervous system is affected". Whether the negative findings of another team of workers¹⁰¹³ suffice to invalidate the above-mentioned contentions and the appealing hypothesis that the cardiovascular disturbances of beri-beri are caused primarily by lesions of the supplying neurosecretory pathways, remains to be elucidated. It is worthy of note that thiamine has been found to inhibit nervous transmission in synapses and end plates^{147a}, and to block the vasoconstrictor action of nicotine^{4320b, 2595a}, but nothing can yet be said regarding the significance of these phenomena for the cardiovascular situation in beri-beri.

Another hormonal feature which may possibly be involved in the cardiovascular syndrome of vitamin B₁ deficiency is an enlargement of the adrenal cortex which has been noted in this condition^{252, 793, 1213, 2065}. However, such enlargements are encountered in a great variety of abnormal circumstances²³⁶⁴ and might have to be considered as secondary and unspecific rather than as an important pathogenic factor.

Pitressin counteracts the peripheral vasodilatation in the Oriental type of beri-beri and thus raises the diastolic pressure but does not significantly affect the systolic pressure level^{1, 3561}.

Treatment

The specific treatment for clear-cut cases of beri-beri consists obviously of the administration of thiamine (daily 100 mg or more of thiamine chloridesubcutaneously or intravenously, in divided doses in the beginning, followed by smaller doses during recovery). The response is sometimes a dramatic one within a few days or even hours, concerning diuresis, congest-

tive symptoms (lit., see^{24,25}), cardiac output^{461, 261}, radiologically determined size of the heart^{250, 251, 261, 222} and electrocardiographic changes^{207, 251, 261}. However, as far as the latter are concerned, a transient aggravation during the early period of treatment has been observed in a number of instances^{225, 242} despite general clinical improvement. It coincided with a temporary marked elevation of the blood pressure and (in one carefully followed case) of the basal metabolism²⁶¹. This suggests that the presumably simultaneous vagal and sympathetic over-activities do not respond to treatment with equal speed but that a more rapid diminution of "muscarinic" cholinergic activity may leave the exaggerated adrenergic effects in control until they too return to normal.

Not all cases of seemingly nutritional heart disease react to the administration of thiamine with the same readiness. Indeed, a rather high percentage of the cases reported in the United States²⁵⁰ showed only slow and incomplete improvement, developing in a matter of weeks or even months, or no improvement at all. Such disappointing results may be due to the coexistence of other forms of heart disease and of more complex nutritional deficiencies or to institution of the treatment at an advanced stage in which irreversible structural damage of the heart muscle is definitely established. In general, it is advisable to combine the thiamine medication with niacin, vitamin K and other vitamin preparations. Digitalis and diuretic drugs, although usually not very effective by themselves²⁵⁰, should not be omitted in severe and partly thiamine-refractory cases. A combination of nutritional deficiencies with degenerative heart diseases is not uncommon and requires considerable individualization of the therapeutic program.

Physical rest is an essential requirement under all circumstances, as it helps to keep sympathetic neuro-secretion at a minimum.

Summary

In its pure, classical form, beri-beri heart disease is characterized by manifestations which correspond predominantly to intensified epinephrine action: increased cardiac output (stroke volume and heart rate), decreased peripheral resistance, increased pulse pressure, "anoxic" electrocardiogram and necrotic lesions of the heart muscle. Besides, there are some indications of a coexisting vagal over-activity (occasional bradycardia, prolongation of P-R, auricular fibrillation). In the hearts of thiamine-deficient animals, both catecholamines and acetylcholine have been found in abnormally high concentrations. Whether the apparent intensifications of neuro-secretory activity of both the sympathetic and parasympathetic cardiac nerves are attributable to certain structural changes which have been observed in these nerves in beri-beri, still remains to be decided. The hemodynamic similarities of beri-beri with the situation prevailing in thyrotoxicosis and

existing signs of vitamin B₁ deficiency in the latter point toward certain analogies between the pathogenic mechanisms of both.

In the Occidental form of beri-beri heart disease, which develops usually in connection with alcoholism, the clinical picture overlaps often with that of other types of degenerative heart disease and with other vitamin deficiencies. Specific treatment with thiamine is therefore not always as successful as in clear-cut thiamine deficiency states, but should be tried in all suspected cases.

Idiopathic Cardiac Hypertrophy ("Cardiomegaly")

Cardiac hypertrophy, especially if occurring in hypertensive patients, is generally ascribed to the mechanical "burden" of increased peripheral resistance. A critical evaluation of this popular concept will be found on p. 457 ff. The present discussion of the clinical entity of "idiopathic cardiac hypertrophy" or "cardiomegaly"⁹²⁶ is intended to serve as an illustration of the fact that hypertrophy of the heart muscle, even of extreme degree, can develop without any demonstrable increase in peripheral resistance or cardiac work.

Definition and General Principles

Cardiac hypertrophy in the absence of arterial hypertension, valvular lesions, malformations, coronary arteriosclerosis or any other possibly explanatory condition, as first described by Jaccard and Gallavardin in 1901⁹²⁷, is designated by the ominous term "idiopathic", meaning of unknown origin. A number of cases, reported in the literature under this caption, may have to be discarded because of the possible involvement of definite pathogenic factors, such as vitamin B₁ deficiency, which had been unknown at the time of their observation. Nevertheless, there still remains a substantial number of instances for which no pathogenic explanation can be given from clinical and pathological data available.

One group, denoted as "congenital", comprises more than 70 published cases of cardiac hypertrophy in infants and young children¹³⁶⁸⁻¹³⁷¹, 70 per cent of which concern infants under one year of age¹³⁷¹. At least 50 cases of

Symptomatology

In the great majority of both "congenital" and adult cases, the patients succumbed suddenly or after one or several periods of congestive failure with dyspnea, cyanosis, and edema.

Some of the cases remained entirely asymptomatic and the cardiac lesion was discovered only at autopsy. If clinical manifestations were present, they

extended over variable periods, ranging from days to years. Anginal symptoms were conspicuously lacking. The blood pressure was normal or low. Paroxysmal tachycardia, auricular fibrillation and extrasystoles were not uncommon. Electrocardiographic changes consisted of depression or inversion of the T-wave, bundle branch block and auriculoventricular block^{926, 2003, 2419, 2772} (personal observation).

Pathology

Hypertrophy from marked to enormous degrees was present in all cases included in the category of idiopathic cardiac hypertrophy. Usually both ventricles were affected with a common prevalence of the left, but there were also several instances in which the anomaly was limited to the right ventricle and auricle (lit., see ²³⁴⁴). Dilatation was frequently seen and often accompanied by a thickening of the endocardium²³²⁴. Degenerative changes of the myocardium, necroses, cellular infiltration and fibrotic scarring are reported as a rather regular feature, even in infancy and childhood^{1825, 1956, 2003, 2419}. They were located prevalingly in the subendocardial layers²⁷⁷². Mural thrombi were often found at autopsy.

Neurohormonal and Hormonal Aspects

No indications were found or even looked for, which might permit any conclusions concerning a possible involvement of neurohormonal or hormonal factors in the pathogenesis of idiopathic cardiac hypertrophy. In one instance concerning a 14-month old infant, "hypersecretion of the chromaffine system" was suspected but not proven⁴⁴¹. On the other hand, hypoplasia of the adrenals was reported in two infants with hypertrophic hearts^{493, 2401}. No data concerning either the adrenal glands or the pituitary are contained in the autopsy reports of the adult cases.

As long as no specific hormone studies and careful histological examinations of the endocrine glands and the cardiac nerves have been carried out, it is impossible to form any definite opinion on the problem in question.

It seems doubtful that the two isolated observations of adrenal hypoplasia should represent a pathogenic principle of the syndrome, especially since adrenal hypofunction causes ordinarily a diminution of the heart size. One would rather be led to believe that in those cases the adrenal changes might have supervened after the enlargement of the heart had been established.

The entire problem of cardiac hypertrophy, as far as hormonal influences are concerned, is still in a state of haziness but it may be worth recalling that enormous cardiac hypertrophies without hypertension occur in acromegaly (p. 165 ff.). Marked hypertrophy is also frequently seen in cases of

pheochromocytoma (p. 86), and of adrenal cortical tumor or hyperplasia (p. 98). In experimental animals, hypertrophy of the heart was elicited by administration of thyroxin (p. 39), of growth hormone (p. 49), and of desoxycorticosterone, the latter only in animals which were forced to exercise¹¹⁹.

Neurohormonal factors appear probable: the occurrence of tachycardias, arrhythmias, anoxic changes of the ECG, sudden death and necrotic lesions, closely resembling those provoked by epinephrine and sympathetic overstimulation (p. 18), suggests the possibility that local neuro-secretory effects may be involved in the development of this "idiopathic" form of cardiac hypertrophy.

Cardiac hypertrophy and degeneration¹²⁰ and electrocardiographic changes, seen in cases of Friedreich's hereditary ataxia²⁷, may belong in the category of neurotrophic cardiac lesions of a possibly related type.

The absence of coronary sclerosis and the stability of the process may account for the general non-occurrence of acute anginal symptoms. One of the writer's patients, aged 44, with normal blood pressure, a very large heart, left bundle branch block and frequent attacks of *angina pectoris*

angina pectoris, an equally obscure syndrome of "idiopathic" myocardial lesions with or without cardiac hypertrophy, in which anginal symptoms are not so uncommon¹²¹.

It is to be hoped that future cases of cardiomegaly will be studied with consideration of the important role played by the endocrine and neuroendocrine systems in cardiac metabolism, function and structure and of its possible implications regarding the phenomenon of idiopathic cardiac hypertrophy.

Treatment

No specific treatment for cardiomegaly and its functional sequelae has yet been evolved. Symptomatic therapy has been conducted along customary lines so far. Modern therapeutic devices, such as radical salt restriction or sympathectomy which are capable of reducing the size of the heart in cases of hypertensive and arteriosclerotic heart disease, do not seem to have been applied yet in cases of cardiomegaly but might well be worth a trial.

Summary

The origin of idiopathic cardiac hypertrophy or cardiomegaly, which occurs in infants, children and young adults, is still completely unknown. However, in view of the existence of cardiac hypertrophy of demonstrably

hormonal and neurohormonal origin, it seems a possibility that some anomaly in the interplay of the pituitary growth hormone, the adrenal corticoids, thyroxin, the adrenosympathogenic catecholamines and the cardiac cellular enzyme systems may form the pathogenic background of this problematic disease, which deserves a thorough study from the endocrine and neuroendocrine points of view.

Athlete's Heart

Definition and General Principles

To avoid confusion regarding the designation "athlete's heart", it should be stressed at the outset of the following discussion that the term is not to be understood as meaning a pathological syndrome. It rather encompasses a number of characteristic cardiovascular changes which develop as a result of prolonged athletic activities and which, although "abnormal" by majority standards, cannot be considered as morbid in the common sense. On the contrary, the usual characteristics of athlete's heart seem to represent optimal conditions in various respects. Their systematic study by Reindell²⁶⁹ and others has contributed indirectly to a better understanding of certain aspects of cardiac pathology as well. Cardiac complications of a pathological nature, which arise occasionally in connection with athletic activities and other types of heavy work, will be pointed out specifically.

The most conspicuous peculiarity of the heart in a considerable percentage of athletes is its enlarged size, as originally observed by Henschen in long-distance skiers in 1899²⁷⁰. Although several earlier workers expressed doubts regarding a direct causal connection between sport activities and cardiac enlargement (lit., see ²⁶⁹), the present consensus of opinions does no longer seriously question the fact that unusually large hearts occur among athletes with greater frequency than in the rest of the healthy population^{71, 74, 149, 170, 190, 259, 300, 301, 310, 370}. It must be admitted, however, that cardiac enlargement is by no means a regular and predictable occurrence and that it does not develop in any fixed proportion relative to the total amount of energy expended. The type of physical exertion appears to be of importance insofar as sports which require a great deal of endurance, such as rowing, swimming, skiing²⁷¹ and long-distance running²⁷², give rise to cardiac enlargement relatively frequently and without much somatic muscular hypertrophy, while a reversed pattern was observed in persons who specialize in maximal energy expenditures for shorter periods, such as weight lifters, sprinters and the like^{159, 273}. However, no hard and fast rule can be claimed to exist in these respects. In fact, normal sized hearts were seen in many marathon runners¹²⁷ and long-distance runners³⁵², and in some athletes even small hearts were found^{231, 274, 314, 370}. In one series the sizes varied between plus 66 and minus 28 per cent of the normal average³⁶⁶; in another group of athletes, the transversal diameters differed up to 5 cm²⁷⁵ (Fig. 72).

The crucial question as to whether the cardiac enlargements seen in athletes

and heavy workers are to be interpreted as an indication of myocardial damage has long been a controversial one (lit., see ²⁷⁶⁹), but can be considered as settled in the negative sense for the great majority of instances^{721, 2273, 2533, 2769, 3001, 3616}. An unfavorable significance is to be attached to cardiac enlargements which develop during vigorous training only in the case of their early appearance (within one to two years)²⁷⁶⁹, or if they become noticeable shortly after an acute extreme over-exertion^{1693, 1694, 2533, 3701}.

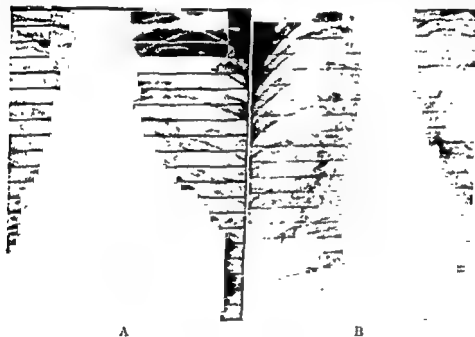


FIG. 72 Size of the heart of (a) an Olympic bicycle race champion and (b) a hurdle race champion (After H. Reindell, *Diagnostik der Kreislaufstörungen*, Ferdinand Enke Verlag, Stuttgart, 1949)

Cardiac damage as a result of excessive acute physical strain has also been demonstrated in animals^{420, 934}.

On the other hand, a reduction of the heart size, immediately following termination of violent exercise, is not an uncommon occurrence in athletes^{26, 410, 750, 1647, 1713, 1765}. It was interpreted as being due to a sudden transient diminution of venous return while the heart is still continuing to beat at an accelerated rate and with subnormal filling¹¹⁹. The enlarged hearts of athletes are able to contract to about normal size under the influence of the Valsalva manipulation (decreased venous back-flow because of augmented intrathoracic pressure)²⁷⁶⁹ after exercise. Temporary diminutions of the heart diameter of as much as 3-4 cm were observed in some cases²⁷⁶⁹ (Fig. 73). These phenomena and the return of the heart size of athletes toward normal dimensions after retirement from sports activities^{2769, 3701}, prove the

fundamentally different character of the cardiac enlargement existing in athletes and that associated with so-called "hypertensive" or valvular heart disease and other pathological conditions of the heart.

During lifetime it is difficult to differentiate clearly between cardiac enlargements produced by dilatation and by hypertrophy. The marked reduction of the size of some large athlete's hearts during the Valsalva test, however, speaks against hypertrophy of the myocardial mass as the prevailing or sole cause of the enlargement. It suggests rather what has



FIG. 72. D. . . . A

B

been designated as "non-organic"¹²⁶¹⁶, "regulatory"²²⁶³ or "tonogenic"^{1406, 2703} dilatation. This type of dilatation differs sharply from the "myogenic" dilatation of the diseased heart muscle in that it is apparently not due to pathological changes in the chemical composition and structure of the myocardium, and in that the heart has not lost its capability of ejecting its augmented ventricular residual volume ("Restvolumen") by means of maximal contraction when the occasion arises. The diseased, more or less flabby "myogenically" dilated heart, although equally large, is unable to perform an analogous dynamic feat.

The fact that the residual volume of the enlarged athlete's heart is increased^{1524, 1764, 2259, 2769} cannot be interpreted as an indication of functional

inferiority. It is consistent with the hemodynamic situation prevailing in such individuals, insofar as their *cardiac output at rest* was found relatively low^{135, 714, 1692, 1916, 2769} on account of both a slow heart rate and a reduced stroke volume.

This latter observation would appear paradoxical, were it not accompanied by findings suggesting a low *total oxygen requirement*^{1377, 2579} and an unusually economical peripheral oxygen utilization. This and the relatively great oxygen uptake from the blood^{362, 3699} enables trained sportsmen to perform physical exercises with a lesser circulatory effort than is the case in the healthy average individual, not to speak of the cardiac patient.

Autoptic reports on the hearts of young athletes are scarce but strongly suggestive of a distinct tendency toward *ventricular hypertrophy*^{422, 1770, 1771, 2769}. Hypertrophy of the heart could also be demonstrated convincingly in experimental animals as a result of enforced physical exertion^{1419, 1481, 2060, 3109}. Despite the general contention that the pathologically hypertrophic heart muscle is metabolically handicapped by an inadequate vascularization relative to the augmented thickness of the myocardial fibers³¹²¹, there are indications that the heart of the trained healthy athlete is privileged also in this respect by possessing a particularly rich capillary supply²⁵⁴⁶. The electron-microscopic finding of intracellular capillaries within the myocardial fibers¹⁷⁷⁷ suggests the possibility of an additional advantageous vascular arrangement, but nothing is yet known about its comparative development in normal and hypertrophic hearts. It may be significant that in the case of an outstanding long-distance ski champion, who had died from an accident, no pathological foci could be detected in the markedly hypertrophic and dilated ventricular walls⁴²².

The *causes of dilatation and hypertrophy of the athlete's heart* are only incompletely understood. The current concept of increased intraventricular pressure as causing pathological dilatation does not seem to apply to the trained heart. At rest, the systolic blood pressure is usually normal or relatively low, and although the diastolic levels are found not far below the upper limit of normal as a rule, there is nothing that would suggest hemodynamic conditions, conducive to a mechanical dilatation of the heart. The venous pressure is not elevated. The cardiac output (rate and stroke volume) is usually lower than normal²⁷⁶⁹. Immediately after severe exercise (measurements taken at the termination of competitive top performances on 24 champions²⁷⁶⁹), the elevation of the systolic blood pressure was found comparatively small (average 150 vs 119 mm), while the diastolic pressure had declined in all but two instances (average 47 vs 73 mm), thus indicating a marked decrease of peripheral resistance. The dynamic achievement of the heart in competitive athletic feats of highly trained individuals has been estimated as being smaller than the cardiac work of a non-trained

person performing 50 genuflections²²⁶. The frequently observed decrease of the heart size during and immediately after exertion²²⁷ furnishes additional evidence against a primarily mechanical, passive origin of the cardiac dilatation in athletes.

The same objections have been raised against the interpretation of cardiac hypertrophy in athletes, as being elicited merely by mechanical factors²²⁸. The "voluntary" hypertrophy of the athlete's heart was contrasted with the "involuntary" hypertrophy associated with hypertension or valvular lesions²²⁹. In the former, a relatively low myocardial oxygen requirement and consumption is assumed to prevail at rest (moderate peripheral resistance, low cardiac output), as well as during exercise²³⁰ (relatively small increase of mean pressure, moderate acceleration; markedly increased stroke volume which requires less oxygen than an equal output achieved by acceleration^{193, 231}). Conversely, the heart of an untrained person or a cardiac patient is believed²³² to consume much more oxygen because it works under less favorable hemodynamic conditions even at rest, possesses a narrower range of accommodation²³³ and, if called upon to support physical exercise, faces a greater peripheral resistance and beats at a higher, more uneconomical rate than the athlete's heart.

Even if we accept the above-outlined, somewhat schematic concept at face value, it cannot be denied that it is more descriptive than explanatory of the differences between the cardiovascular system of the trained athlete and that of his sedentary fellow-man and that it leaves the "Why?" in suspense. We can hardly hope ever to reach the ultimate answer to this question, but one step further down into the depths of causality seems accessible and, indeed, has already been ventured by Reindell and his associates by abandoning the purely mechanistic approach and by paying due attention to nervous and neurohormonal factors which will be discussed in the following section.

Neurohormonal and Hormonal Aspects

While a pathogenic prevalence of adrenosympathetic neuro-secretory overactivity was emphasized in the discussion of various pathological conditions of the heart, we shall have to concentrate our attention primarily on vagal cholinergic mechanisms where the quasi supernormal peculiarities of the athlete's heart are concerned.

It will be well to recall the fact that acetylcholine, the chemical neural transmitter which is physiologically liberated by the vagal nerve endings is capable of exerting directly anti-adrenergic effects²³⁴. It

inferiority. It is consistent with the hemodynamic situation prevailing in such individuals, insofar as their *cardiac output at rest* was found relatively low^{135, 714, 1692, 1848, 2789} on account of both a slow heart rate and a reduced stroke volume.

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tions. The combination of a rise of the systolic pressure with a fall of the diastolic level (decreased peripheral resistance and increased stroke volume; see preceding section), suggests vigorous epinephrine action upon the vascular system and the heart. Cardiac acceleration was found not to be marked immediately after moderate exertion and to disappear quickly^{74, 75}, but maximal effort was often accompanied by considerable tachycardia which not infrequently showed a tendency to decline over a comparatively long period (up to 25 minutes) after termination of exercise⁷⁶ (Fig. 74). It seems possible that this behavior is caused by a prevention of the vagotropic Bezold-Jarisch reflex from taking effect, as a result of the temporary post-exercise diminution of the heart size (see preceding section), since this

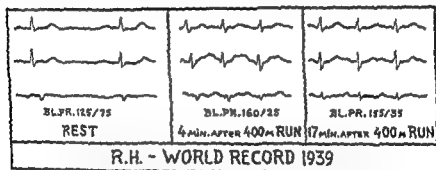


Fig. 74. Electrocardiogram and blood pressure before and after extremely severe exercise (world record breaking 400 meter run)
(Re-drawing after H. Reindell: Diagnostik der Kreislaufkrankheiten, Ferdinand Enke Verlag, Stuttgart, 1919)

reflex is believed to be activated by a stretching of the cardiac muscle fibers^{77, 78}.

Increased adrenergic activity during and immediately after severe exercise of athletic individuals is also manifested by a frequently observed shortening of the T-wave⁷⁹. However,

connection with especially strenuous physical efforts which were associated with

conscious loss of teeth, tonsils, after tobacco smoking, sexual excesses, etc. It seems worthy of note that none of the hearts which displayed these abnormalities was enlarged⁸⁰. Flattening or inversion of T1 and T2 and depression of ST

must be emphasized, however, that the exact opposite of the just-mentioned reactions may likewise be provoked by administration of acetylcholine, depending on dosage and on the state of adrenergic-cholinergic balance, existing in the test subject from the beginning. Persons of the "vagotonic" type (with slow resting heart rate and other criteria) were found to respond in the above-outlined anti-adrenergic fashion, while those of the "sympathicotonic" type (with rapid heart rate and especially cases of thyrotoxicosis), on the contrary, reacted with further cardiac acceleration, depression of the T-wave, marked elevation of the mean blood pressure and oxygen consumption¹⁵⁹¹. This contradictory and rather confusing behavior is due to the "amphotropic"⁶⁵³ function of acetylcholine, i.e., to its dual action in producing both direct vagal (muscarinic) effects and in simultaneously inducing the liberation of its adrenergic antagonists^{963, 1341}. The result in the individual case will depend on the delicate equilibrium between these mechanisms which, according to a hypothesis of Danielopolu⁶⁵⁸, may be even further complicated by a reversed liberation of acetylcholine through adrenergic action.

With the complexity of the *adrenergic-cholinergic interplay* (which probably represents the key to many cardiovascular metabolic and pathogenic phenomena) in mind, and with awareness of the oxygen-sparing effect of direct vagal action, it will be possible to approach the problem of cardiovascular training and of its end result, the supremely efficient heart of the healthy athlete.

The most striking evidence of cholinergic vagal preponderance in the athlete's heart is its slow action at rest^{620, 1567, 1926, 2769, 3596} which has been found as low as 32 and 38 beats per minute respectively in two runners^{2769, 3596}. It is sometimes (in about 16 per cent)²⁷⁶⁹ associated with a prolonged P-Q interval^{620, 1567}, especially in long-distance skiers, cyclists, wrestlers²⁷⁶⁹ and heavy laborers²³⁶². Readings of 0.32 seconds and more have been obtained in several cases²⁷⁶⁹. The T-wave is usually tall, particularly in lead II^{1926, 2769, 3307}. In a large series of athletes who were observed over many years²⁷⁶⁹, there was not a single instance of progressive flattening or inversion of T2. In 850 resting electrocardiograms of athletes, there were only 8 instances of auricular or ventricular premature beats²⁷⁶⁹. In the erect position, the T-wave changes were found to be insignificant²⁷⁶⁹. Interestingly, the vagal preponderance proved less conspicuous in female athletes than in males¹⁹³⁰.

While the above-enumerated criteria plus the low cardiac output and low total oxygen consumption (see preceding section) indicate a strong vagal influence upon the athlete's heart during rest, this *vagal preponderance yields during severe exercise to sympathetic stimulation*, however, apparently in a manner which still safeguards optimal metabolic and dynamic condi-

Pathological Complications

The emphasis which was placed in the preceding section on the advantage of athletic activities in gradually shifting the neurovegetative equilibrium of the cardiovascular system toward the vagal side, must not be misunderstood as implying that vigorous physical effort is under all circumstances conducive to an improvement of cardiovascular efficiency. Again, the potentialities of the amphitropic action of acetylcholine and the divergent responses of primarily vagotonic and sympathotonic individuals to acetylcholine^{178 181} have to be recalled. It seems intelligible that a person with constitutional or acquired adrenergic prevalence, as in thyrotoxicosis, hypertension, angina pectoris, vitamin B₁ deficiency, etc., will respond to cholinergic stimulation with intensified oxygen-wasting adrenergic side-reactions rather than with a preponderance of vagal oxygen economy.

Enforced heavy exercise in untrained or diseased individuals, or the acute imposition of an exceptionally excessive effort even on a fairly well-trained person, must be expected to evoke the potentially pathogenic effects of strain, i.e., of overwhelming hypoxia-producing adreno-sympathetic catecholamine action, unopposed by a sufficient oxygen-sparing vagal counterbalance (Fig 4B, p 374). The eventually catastrophic effect of such an unchecked influx of adrenergic neurohormones into the myocardium seems to be illustrated by the writer's observation of a seemingly healthy young athlete (sprinter) who died unexpectedly in his sleep and whose otherwise normal heart muscle contained an excessively high concentration of catecholamines²⁶⁷.

The pro's and con's regarding the admission of young individuals to intense training in various sports have been ably pointed out by Wilce²⁶⁸. A practical fitness test, based solely on the duration of exhausting exercise and on the speed of subsequent cardiac deceleration¹⁶² was devised for the selection of suitable candidates for rigorous physical training. Wilce's admonition that "participation in sport should be encouraged in every way but only under alert, accurate and liberal medical supervision" appears timely in a generation which seems determined to settle down in front of its television sets for an existence of both muscular and cerebral inertia.

Summary

The heart and circulation of the healthy athlete differ from those of the average non-trained individual in the following respects: (a) the heart is often dilated but nevertheless capable of maximal contraction during exercise ("tonogenic" dilatation), cardiac enlargement is particularly common in connection with endurance sports but small hearts are also seen in some athletes, (b) at rest, the cardiac residual volume is large and the cardiac

this may be attributable in part to greater skill in using a smaller mass of muscles to greater advantage²⁷², it should also be remembered that vagal cholinergic activity tends to depress oxygen consumption.

Taking all in all, it appears that the athlete and heavy laborer is favored not only by a general vagal preponderance which protects his cardiovascular system from the hazards of sympathogenic oxygen waste and tissue hypoxia while at rest, but also by an unusual flexibility of the interplay between the adrenergic and cholinergic neurogenic antagonists. This permits him to mobilize his adrenergic mechanisms when required for maximal action but even then with a markedly dampening influence of his vagus upon cardiac energy expenditure and oxygen consumption. The result is increased cardiac work efficiency with a minimum risk of pathogenic exhaustion.

As far as the phenomenon of "tonogenic" cardiac dilatation in athletes is concerned, Reindell²⁷⁹ advanced the interesting theory that it might be caused by an active alteration of the ventricular muscular tone under vagal influence, consisting of a postulated "negative tonotropic" effect of the vagus, as opposed to "positive tonotropic" sympathetic action. It is difficult to prove the correctness of this concept experimentally with normal hearts of animals since the "amphotropic" cholinergic action is inevitably accompanied by secondary adrenergic side effects of a major or minor degree. The trained heart, however, may conceivably differ from the average animal heart by its very tendency to suppress these adrenergic side effects and to permit the prevalence of primary vagal action, not only regarding heart rate, stroke volume and auriculo-ventricular conduction, but also concerning general myocardial tonus, thus giving rise to "regulatory" or "tonogenic" dilatation which can be temporarily replaced by adrenergic reduction of the heart size during exercise.

The intricacy of these subtle interactions between opposing forces may serve as a clue to the reasons for which some trained individuals develop marked cardiac dilatation while others don't.

The problem of hypertrophy of the heart muscle in connection with athletic activities can hardly be considered from the point of view of neuro-hormonal factors alone. Here, the participation of various other hormones (thyroid, pituitary, adrenocortical) must be thought of, as intimated in the chapters on "idiopathic cardiac hypertrophy" (p. 444) and on "hyperten-

ences in the origin of athletic cardiac hypertrophy. Only one statement can be made with assurance, namely that the traditional one-sided mechanistic concepts have proven inadequate also in regard to the explanation of this particular type of hypertrophy.

"Hypertensive" Heart Disease

Definition and General Principles

The widespread usage of the term "hypertensive" heart disease, with the tacit implication that this particular cardiac syndrome is not only frequently observed in hypertensive persons but actually caused by the hypertensive state, requires some introductory remarks.

In the first place, it must be stressed that none of the phenomena, the combination of which is incorporated in the collective term "hypertensive" heart disease, and which will be individually discussed in the following sections, is to be regarded as specific for this cardiac syndrome. Neither the dilatation of the heart muscle nor its hypertrophy, neither the electrocardiographic and functional nor the histologic cardiac changes, occurring as constituents of "hypertensive" heart disease, can be claimed to be limited to this disease alone and to occur exclusively in association with temporary or sustained elevations of the blood pressure.

Moreover, the same can be said concerning the fully developed cardiac syndrome of "hypertensive" heart disease. It is paralleled by its sympto-

logical manifestations in some normotensive cases of acromegaly. In other words, the complete cardiac syndrome of "hypertensive" heart disease occurs also in the total absence of arterial hypertension.

It has often been said that "hypertensive" heart disease is caused simply by the abnormal "load" or "burden" of increased peripheral resistance. This conception is contradicted by the above-mentioned instances of, as it were, normotensive hypertensive heart disease" and even more specifically by observations which show that certain therapeutic measures can abolish the signs and symptoms of "hypertensive" heart disease in hypertensive patients despite failure to diminish the hypertensive circulatory "load" (p. 414 ff.). These striking inconsistencies with the mechanical load theory, together with "lack of correlation" between the severity and duration of hypertension and the development of cardiac disease,

cannot be state as such

... more than the

This does not mean, however, that the hemodynamic situation, which exists in the hypertensive individual, can be entirely disregarded as a contributory element. On the contrary, it seems most likely that certain initial

output small; general oxygen consumption was found reduced; the heart rate is low, the atrioventricular conduction (P-Q interval) sometimes prolonged, the T-waves are often high, hardly ever depressed; (c) during exercise, the systolic pressure rises only moderately, the diastolic pressure falls, the cardiac output is greatly increased, acceleration may be marked; the increase of general oxygen consumption is relatively small; (d) immediately after exercise, the heart size may temporarily appear reduced; cardiac deceleration is usually prompt except in some instances of extreme effort; electrocardiographic signs of myocardial hypoxia occur only as rare exceptions and are usually ascribable to coexisting infections, etc.; (e) post-mortem findings indicate a tendency toward hypertrophy but histological lesions seem to be scarce.

Most of the above-enumerated peculiarities are attributable to an *acquired vagal preponderance which yields to adrenergic effects during exercise, however apparently in such a manner that adreno-sympathogenic myocardial hypoxia is prevented and optimal cardiac oxygen economy guaranteed.*

Pathological complications may arise in case of unrecognized pre-existing cardiovascular disease and of excessive acute over-exertion in insufficiently trained individuals.

The various characteristics of the athlete's heart can be considered as examples of the complex interplay between adrenergic and amphotropic cholinergic neurosecretory effects, with the latter tending toward the vagal (muscarinic) side, thus endowing the athlete's heart with superior qualities of dynamic efficiency, endurance and metabolic safety

Symptomatology

Fatigue, shortness of breath and palpitations are common symptoms of the advanced stage, forecasting impending cardiac failure. In some instances, the blood pressure level decreases with progressing decompensation, which has to be regarded as a prognostically ominous sign²²⁷.

Roentgenologically detectable cardiac enlargement with left ventricular preponderance does not include the left auricle, the pulmonary circulation and the right heart, as long as cardiac compensation is maintained. Left auricular dilatation, pulmonary congestion, dyspnea, and attacks of pulmonary edema are indicative of supervening left ventricular insufficiency which may ultimately develop into failure of both ventricles, general congestion, and death.

A clear clinical distinction between ventricular dilatation and hypertrophy is not possible, but certain details of the cardiac silhouette, the sequence of developing alterations, an occasional heaving apical impulse, and electrocardiographic changes may permit some tentative conclusions. Left axis deviation of the electrocardiogram is not specific enough to reveal left ventricular hypertrophy with certainty. An additional flattening or inversion of T and depression of S-T in the limb leads I or I and II, as well as in the chest leads, facing the surface of the left ventricle^{218, 220}, establishes the so-called "left ventricular strain pattern" which, however, resembles the electrocardiogram obtained in various other conditions involving myocardial hypoxia. It is neither specific for hypertensive heart disease nor necessarily dependent on the existence of a mechanical ventricular "strain"²¹² and therefore of only limited diagnostic value.

Pathology

Cardiac hypertrophy, especially of the left ventricle, with or without dilatation, although the most characteristic autopsy finding of hypertensive heart disease²⁴⁵, does not show any direct quantitative relationship with the severity¹³⁰ or duration²⁴⁴ of a coexisting hypertension, nor does it by itself justify the posthumous conclusion that hypertension must have been present during lifetime. An increase of the myocardial mass is also frequently seen in the hearts of individuals with atherosclerosis but without evidence of hypertension²⁴⁶.

Coronary sclerosis is so frequently encountered in cases of hypertension^{247, 248, 249} that it has been suspected as being largely responsible for the development and fatal outcome of hypertensive heart disease^{249, 250}. On the other hand, there are those who doubt a pathogenic significance of the minor coronary sclerotic lesions found in the majority of hearts of hypertensive individuals^{250, 251, 252, 253, 254, 255}. The writer feels inclined to agree with

predisposing changes develop in the heart muscle as a result of its presumable metabolic reactions to an altered hemodynamic status, combined with those neurohormonal, hormonal and other biochemical influences which are believed to be responsible for the hypertensive state per se (p. 263 ff.).

Some investigators distinguish between the by far most common "*resistance hypertension*" (p. 277) and a so-called "*minute volume (cardiac output) hypertension*" (p. 278). Both of these types are associated with an increased dynamic performance of the heart muscle, but it is mainly the resistance hypertension which imposes on the myocardium the mechanical strain of an increased diastolic pressure, probably resulting in an augmentation of cardiac metabolism^{3052, 3229}. The fact that a roentgenologically visible cardiac dilatation can persist in hypertensive individuals for long periods of time without any indications of left auricular and pulmonary congestion³⁷⁰³, suggests a comparatively high degree of dynamic efficiency of the primarily dilated left ventricle ("tonogenic" dilatation).

During the stage of compensation, the cardiac output of hypertensive persons^{447, 1943, 2769, 2775} does not differ very significantly from normal, except in some instances of increased heart rate and stroke volume ("minute volume hypertension") (lit., see ²⁷⁶⁹). Certain early changes of myocardial dynamics regarding the isometric and isotonic contraction periods are of a minor degree only²⁹⁹; the venous pressure and right atrial pressure remain unchanged²⁹⁴ and congestive cardiac symptoms may be entirely absent for periods of many years.

If and when signs of congestive failure of the dilated heart supervene, it can be concluded that a transition from "tonogenic" to "myogenic" dilatation has taken place and that an efficiency-reducing metabolic damage of the heart muscle has become established.

Cardiac hypertrophy, secondary (myogenic) dilatation and ultimate insufficiency are three outstanding pathological manifestations of hypertensive heart disease, the pathogenesis of which we shall have to investigate. As mentioned above, a specific and exclusive causal relationship between the phenomenon of arterial hypertension on one hand and the signs of advanced hypertensive heart disease on the other appears doubtful, even though it is generally assumed to exist because of the admittedly impressive numerical coincidence of the two conditions⁹²⁹. Sixty to seventy-five per cent of all hypertensive individuals die from cardiac complications, among which cardiac failure ranks first (lit., see ¹⁰⁶⁰), and in accordance with traditional mechanistic thinking, it seemed logical enough to accrue the high blood pressure level per se of causing all the manifestations of hypertensive heart disease. Closer scrutiny has made this reasoning appear inadequate, however, and other more probable alternatives have to be considered which will be discussed further below.

As will be seen in the following discussion, it is not yet possible to demonstrate directly the specific role of any of the hormones under consideration in the pathogenesis of hypertensive heart disease. Nevertheless, there exist many strongly suggestive findings which may at least establish the foundations for a promising investigative approach to this difficult problem.

Cardiac hypertrophy and degenerative myocardial changes, analogous to those characteristic of hypertensive heart disease, have been produced experimentally in animals by repeated injections of epinephrine^{175, 184, 191, 192, 193, 215, 269, 274} and occur as common complications in clinical cases of pheochromocytoma^{205, 124, 142, 187, 179, 195, 262, 311, 314} whose pathogenic kinship with essential hypertension regarding over-activity of sympathomimetic catecholamines is being increasingly appreciated^{117, 119, 124, 217} (Fig. 75)

In which specific way the sympathomimetic amines stimulate myocardial cell hypertrophy is unknown, but it seems possible that their calorigenic activity may be a factor in conjunction with increased cardiac work. The

above results, suggests that those sections of the heart which expend the most energy and consume the largest amounts of oxygen are the ones which develop also the most pronounced responsiveness to the cell growth-promoting effect of the somatotrophic hormone of the pituitary. This principle was experimentally illustrated by the fact that the hearts of hypophysectomized animals which had been put under mechanical strain (partial ligation of the aorta) did not become hypertrophic, while marked cardiac hypertrophy developed when the pituitary gland was re-implanted²¹¹.

The thyroid hormone, whose probably most important effect on the heart consists of a potentiation of the metabolic activity of the sympathomimetic catecholamines (p. 35), has been found to sensitize the heart muscle to the hypertrophy-producing action of the pituitary gland²¹¹. On the other hand, the pituitary growth hormone is believed, in turn, to sensitize the heart to hypertrophy-producing^{207, 208, 228} deoxycorticosterone²⁰¹. The effect of the latter is also markedly enhanced by physical exercise (catecholamine action)²¹³. In view of these observations and concepts, one may with some justification speculate on the following sequence of events in the development of cardiac hypertrophy in connection with hypertensive heart disease.

- (a) Increased peripheral resistance elicits an augmentation of myocardial metabolism^{71, 102, 229}, which is inherent in the resulting increased dynamic performance
- (b) Co-existing sympathetic over-stimulation (in neurogenic hyperten-

Friedberg's assumption that a common mechanism might be operative in the causation of both hypertensive heart disease and coronary sclerosis rather than that either one of the two would cause the other, except that an established chronic myocardial ischemia, due to advanced coronary sclerosis, may make the myocardium metabolically more susceptible to the hypertrophy-producing hormonal and neurohormonal influences (see below)

It has been stated^{130, 131} that coronary atheromatosis does not necessarily produce a significant narrowing of the coronary vascular bed. In fact, studies carried out with filling of the coronary tree¹³⁰ showed that the moderately sclerotic coronary arteries of hypertrophic hearts from hypertensive individuals may be unusually wide, and the conclusion was reached that in most cases of hypertensive heart disease the coronary system is sufficiently enlarged to prevent vascular ischemia as a cause of cardiac failure¹³⁰. Signs of clear-cut myocardial infarction are only rarely seen in the hearts of persons who had displayed severe hypertension but foci of fibrotic degeneration are a common finding, regardless of the presence or absence of coronary occlusions¹³⁰.

The degree of *myogenic cardiac dilatation*, which had existed during lifetime and which had constituted a diagnostically important clinical corollary of cardiac failure in many hypertensive patients, cannot always be properly evaluated on the autopsy table in contrast to hypertrophy which, in turn, often eludes clinical detection. It can be said, however, that a lack of dilatation post-mortem is observed mainly in the cases which had ended in death from causes other than cardiac failure¹⁰⁰, while in the cases of death from congestive hypertensive heart disease, both hypertrophy and dilatation are found, as a rule.

Neurohormonal and Hormonal Aspects

In the preceding sections, several points were raised to motivate the writer's opinion that the manifestations of so-called hypertensive heart disease are not caused simply by the mechanical load of the elevated blood pressure (peripheral resistance). Neurohormonal and hormonal biochemical influences upon the heart muscle deserve primary consideration as important additional pathogenic factors, (a) because all manifestations of hypertensive heart disease can be experimentally duplicated by administration of neurohormones and hormones, (b) because these very manifestations are known to occur also as specific complications of certain clinical endocrine syndromes, and (c) because neuroendocrine and endocrine factors are believed to be prominently involved in the pathogenesis of essential hypertension which is pathogenically coordinated to hypertensive heart disease but probably not its necessary causative prerequisite.

sion) further increases the metabolic processes in the ventricular musculature but renders them dynamically less efficient under the combined oxygen-wasting influence of the sympathogenic catecholamines and the thyroid hormone

(c) The intensified metabolic activity of the myocardial cells makes them abnormally susceptible to the growth-promoting action of the pituitary somatotrophic hormone and of adrenal mineralocorticoids.

This hypothesis appears consistent with Schumann's statement that hypertrophy of the heart muscle occurs always when cardiac metabolism is constantly increased³⁶² and with the observation of cardiac hypertrophy in growing rats which were kept at a low oxygen pressure³⁶³. Recently published estimates of cardiac oxygen consumption in man, which are based on coronary sinus catheterization³⁶⁴ and on indirect calculations of the unknown myocardial mass suggest normal values for hypertensive patients and for other conditions with increased peripheral resistance. These findings are difficult to reconcile with the results obtained in animal experiments in which the cardiac mass was accessible to exact direct measurement, and their validity remains open to question.

The complexity of the mechanical, metabolic and hormonal factors, which supposedly participate in the process of cardiac hypertrophy, might account for the irregularity of its quantitative relation to the degree and duration of the hypertensive state³⁶⁵. The disproportion between cardiac hypertrophy and renal involvement in hypertensive individuals³²³ suggests a greater importance of neurohormonal and hormonal factors in its origin, compared with that of the problematic renal precursor agents.

The *electrocardiographic changes* appearing in hypertensive heart disease progress often beyond a mere left axis deviation and prominent S-

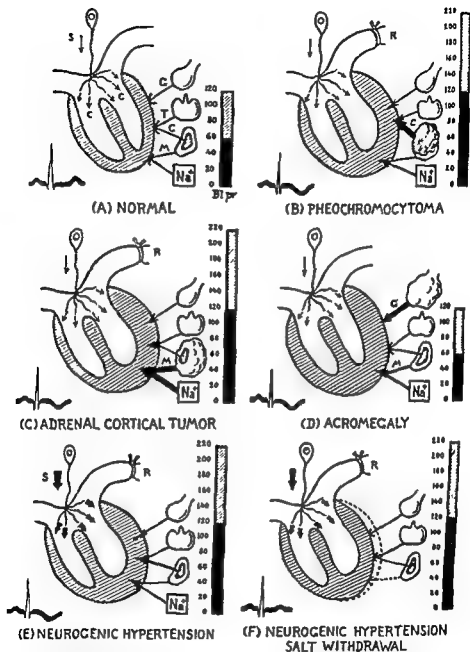


FIG. 75 Tentative Representation of Neurohormonal and Hormonal Factors Probably

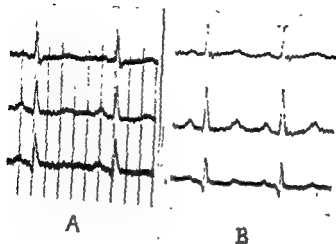


Fig 77

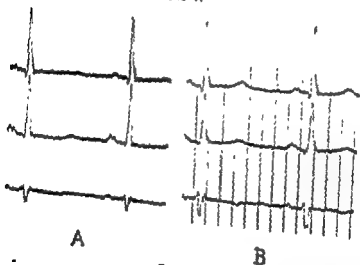


Fig 78

(1) pr 200/120
(After O. Bayer, L. Bodin, H. Boemingham and S. Elfert, *Ztschr f klin Med* 146
607, 1950)

(3) More or less striking normalizations of the pathological electrocardiogram after lumbodorsal or total sympathectomy have been observed in many cases of hypertensive heart disease despite persistence or even further elevation of the hypertensive blood pressure level (77, 78), so that various investigators arrived at the con-

and the T-wave^{290, 295, 463, 919, 1357, 2245}. They are generally considered as indicative of myocardial hypoxia. That they are not essentially caused by the hemodynamic "burden" of increased peripheral resistance is suggested by the following facts:

(1) There is no recognizable connection between the duration of hypertension and the development of electrocardiographic anomalies⁹¹⁹. Although a certain relationship seems to exist between the occurrence of T-wave changes and the degree of diastolic hypertension^{919, 978, 1357}, this does not suffice to prove a direct provocation of the former by the latter. Moreover, analogous electrocardiographic alterations are frequently observed in normotensive individuals during states of myocardial hypoxia (coronary sclero-

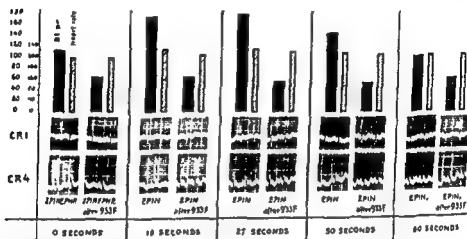


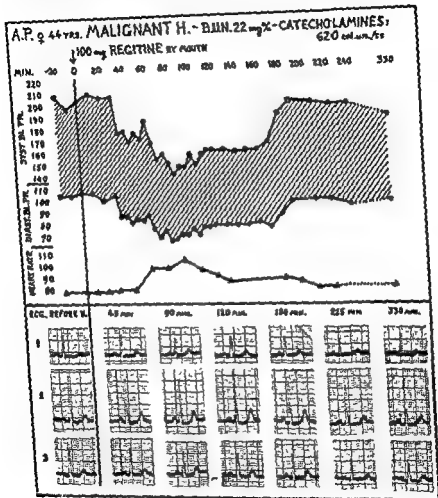
FIG. 76 Epinephrine-induced inversion of T wave undiminished by 033F (benzodioxane) despite abolition of pressor effect (black bars) of intravenously injected epinephrine in the atropinized cat

(After W. Raab and E. Lepeschkin, *Acta med Scandinav.* 133: 81, 1950)

sis, low oxygen breathing, infusion of epinephrine, etc.) and in idiopathic cardiac hypertrophy²⁷¹².

(2) Experimental studies carried out by the writer and E. Lepeschkin^{2712, 2713} in humans and animals failed to reveal any proportionality between the pressor and the electrocardiographic effects of infused epinephrine and nor-epinephrine. In fact, the complete abolition of the pressor action of these hormones by benzodioxane, prisol, etc. did not in the least interfere with their ability to produce depressions or inversions of the T-waves (Fig. 76). Similar results were obtained by others¹¹²⁹. N-isopropyl-epinephrine (isuprel) which does not raise the blood pressure elicits electrocardiographic changes analogous to those produced by epinephrine^{2712a}. Hence, the catecholamine-induced, hypoxic changes of the electrocardiogram can be regarded as totally unrelated to the blood pressure level and as the direct result of a local biochemical action on myocardial metabolism,

tirely depleted of catecholamines²⁸⁵ (Fig 70, p 432), while nine of out 16 hearts of non-sympathectomized hypertensive individuals contained



(180 minutes)

(After W. Raab and S. J. Yaffe, unpubl.)

abnormally high catecholamine concentrations²⁸⁶. The appearance of both blood pressure elevations and marked hypovic electrocardiographic anomalies after cerebral injury²⁸⁷ was interpreted as being due to sympathogenic effects, possibly caused in part by discharges of the cerebral sympatho-

clusion that the improvements of the electrocardiogram and possibly also of other features of hypertensive heart disease, following sympathectomy, are in principle not causally connected with the behavior of the blood pressure^{1821, 2441, 2495, 2712}. A mutual independence of cardiac muscular dynamics and the electrocardiogram in hypertension has likewise been emphasized²⁹⁷. The same is suggested by the occasional disappearance of electrocardiographic abnormalities in hypertensive patients who were treated with a low sodium diet but did not respond with a lowering of the blood pressure^{417, 1743, 1744, 3512}. The duration of the normalizing effect of sympatholytic drugs on the "hypoxic" electrocardiogram in hypertensive heart disease was occasionally found to exceed that of the blood pressure-lowering action (Fig. 79)²⁶⁹².

In view of the above-enumerated observations, which tend to disprove the conception that the S-T and T-wave depressions in hypertensive heart disease are caused by the "load" of the elevated blood pressure, the question arises as to what positive evidence can be adduced for the interpretation of these electrocardiographic anomalies, as being attributable to an exaggerated catecholamine action on the heart muscle.

A number of points which speak in favor of an increased sympathetic neurosecretory activity in the neurogenic phase of essential hypertension in general, has been discussed on p. 263 ff. As far as the heart in particular is concerned, it seems appropriate to emphasize the essential identity of the electrocardiographic phenomena of hypertensive heart disease with those produced by injected or infused epinephrine (p. 12, 14) and by sympathetic stimulation (p. 14). The occurrence of shortened P-R intervals in hypertensive individuals²⁹³⁵ may also be mentioned as a criterion of increased sympathetic activity.

Reported improvements of the electrocardiographic "strain pattern" after administration of certain sympatholytic ergot preparations^{299, 1701, 2994, 3213} and particularly as a result of sympathectomy^{174, 345, 1337, 1831, 2495, 2852, 2946, 3150, 3605}, point in the same direction. Even though most of the sympathectomies which are performed for the treatment of arterial hypertension do not include denervation of the heart itself, they inactivate large numbers of neurosecretory post-ganglionic sympathetic fibers and deprive the adrenal medulla of its secretory innervation. It is worthy of note that the urinary excretion of sympathomimetic catecholamines was found markedly reduced after sympathectomy in hypertensive patients¹¹⁸¹, and that a marked diminution of the catecholamine concentration in the hearts of sympathectomized animals was observed by the writer in collaboration with the late Dr J. P. Maes²⁷¹⁴ and by Goodall^{1296a}. Likewise, the heart muscle of one sympathectomized hypertensive patient proved almost en-

existing coronary sclerosis and the supposed impairment of myocardial cell oxygenation because of fiber thickening must be considered as further contributing factors.

Certain superimposed functional episodes and complications, such as auricular fibrillation and pulmonary edema, resemble the toxic effects which can be experimentally induced by large doses of epinephrine. These aspects as well as the conspicuous analogies between the chemical composition of the failing hypertensive heart and the heart muscle which had been exposed to the influence of toxic doses of epinephrine, will be discussed in the chapter on congestive heart failure (p. 491).

The comparative rarity of anginal symptoms in conjunction with advanced hypertensive heart disease and with cardiac failure in general^{1100, 1111} was tentatively explained by the usual reduction of physical activities of these patients. However, beyond this factor there seems to exist some deeper rooted incompatibility between congestive failure and anginal pain. One might think of a possible protective effect of the vagotropic cardio-vascular reflex mechanism which is believed to originate in the distended heart muscle^{1100, 1111}. Moreover, the profoundly altered metabolic situation in the

transition from a sudden transition from approximate normalcy to hypoxia in the heart muscle

A probable participation of the thyroid hormone as the mechanism

cases of hypertensive heart disease (see following section).

Treatment

Much that was said about the treatment of arterial and malignant hypertension in the chapter on hypertensive heart disease, but because lowering of the blood pressure would constitute a necessary prerequisite of cardiac improvement, but rather because of the influence, exerted by various therapeutic procedures simultaneously on the pathogenic mechanisms which both arterial hypertension and "hypertensive" heart disease have in common.

refractory to otherwise potent adrenergic blocking agents, such as dibenamine, prazosin, benzodioxane and the ergot alkaloids, regarding inhibition of the chronotropic and inotropic effects of

mimetic amine enkephalin²⁶³², into the circulation²⁶²⁵. On the other hand, normalization of hypoxic electrocardiographic changes was seen in pheochromocytoma patients after removal of the tumor^{2605, 2719}.

In spite of the fact that positive indications for a prominent role of adrenal mineralocorticoids in the pathogenesis of essential hypertension could be detected only in a limited number of cases by the sweat test and by hormone assay^{676, 2593}, there are reasons to suspect a more general involvement of adrenal cortical activity in the origin of hypertensive heart disease. The cardiac symptomatology of hyperadrenocorticism (Cushing's syndrome)^{1100, 2367, 2342, 2192, 3157, 3631} strikingly resembles that of hypertensive heart disease, and all clinical characteristics of the latter, electrocardiographic²⁶⁶³, roentgenologic^{2663, 2701} and functional^{626, 969, 2129, 2135, 3180, 3290, 3618}, have been duplicated by administration of DCA. Selye's experimental results in animals²⁰⁷¹ which demonstrated a cardiac hypertrophy-promoting effect of DCA, especially in combination with extra salt intake²⁰¹⁶ and with growth hormone administration²⁰⁹¹, caused him to include the syndrome of hypertensive heart disease in the category of the "diseases of adaptation"¹²⁰⁷.

Significantly, the intracellular deposition of sodium in the myocardium under the influence of DCA^{661, 2120, 2613} is paralleled by the finding of abnormally high intracellular sodium concentrations in the hearts of patients who had succumbed to congestive failure³⁶²⁹ (see also p. 513). Considerable increases of intracellular sodium have also been found in the hearts²¹⁶⁰ and entire bodies²⁹³⁹ of animals with experimental renal hypertension. This might be consistent with the hypothesis¹⁰⁷³ that mineralocorticoids are retained in the circulation in the case of impaired renal excretory function.

The often striking electrocardiographic, as well as functional improvement of the diseased hearts of hypertensive patients during the intake of a sodium-poor diet^{767, 1713, 2744, 3617}, serves as an additional indirect argument in favor of a contributory involvement of the adrenal cortex in the pathogenesis of hypertensive heart disease, since the mineralocorticoids are believed to exert their detrimental cardiovascular effects largely by means of their influence on intracellular sodium concentration²⁶⁰⁹. Finally, impressive normalizations of the cardiac symptomatology were achieved in severely hypertensive patients by subtotal or total bilateral adrenalectomy (p. 318).

Myogenic dilatation of the hypertrophic heart muscle, leading to congestive failure, occurs in the advanced stages of hypertensive heart disease as the end result of the metabolic and structural damage, presumably wrought on the heart muscle by the above-discussed neurohormonal and hormonal biochemical influences: hypoxia and deranged electrolyte distribution. Co-

dorsal sympathectomy were observed over prolonged periods in one-third to one-half of the cases^{17, 1250, 1257, 252}. Occasionally, these diminutions of the roentgenographic silhouette of the heart may have been accentuated by orthostatic hypotension during the examination, but in some instances the reduction in size was noted despite unchanged persistence of the hypertension¹²⁵⁷.

Depending on the hemodynamic type (resistance hypertension or minute-volume hypertension), the circulatory alterations caused by sympathectomy manifested themselves prevalently as a diminution of either the peripheral resistance or of the cardiac output⁷³.

Altogether, the long-range results of extensive sympathectomy regarding the cardiac complications of hypertension²⁰⁶ and regarding the period of survival^{1248, 2162, 3110} appear to be definitely worthwhile in carefully selected cases.

Performance of sympathetic surgery in hypertensive patients with medically intractable congestive failure is usually being discouraged^{126, 177, 391, 1257, 2115, 3179}, but in some instances³⁹¹, especially in the experience of Mexican clinicians³¹², remarkable and prolonged improvements have been achieved in the majority of severely decompensated patients so that the prevailing conservative attitude may possibly require a revision in this respect.

Inactivation of the thyroid gland cannot be expected to produce any decisive improvement of the hypertensive state²⁷ as such. With only few exceptions¹⁵², antithyroid treatments have, therefore, not been applied specifically for either hypertension or hypertensive heart disease in the compensated stage. However, among the euthyroid patients in congestive failure who were subjected to such procedures there were some

... are not numerous, but they seem to be consistent with the view that the thyroid participates in the manifestations of hypertensive heart disease as the physiological potentiator of the hypoxiating cardiotoxic effects of the adreno-sympathogenic catecholamines (p. 35) and that its elimination acts favorably by *devenenizing* the heart muscle to these toxic influences, regardless of the behavior of the blood

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... sodium intake to the lowest possible amount (about 180 mg sodium per day), especially by using Kempner's rice diet. Kempner himself⁷²⁰ reports, apart from an increase in the angle of the electrical axis, an elevation of the originally low, diphasic or inverted

injected or secreted catecholamines, is amply established by animal experimentation (lit., see ²⁴³⁴). It seems to preclude a strikingly beneficial action of these drugs in hypertensive heart disease from the beginning. Some of them are actually contraindicated because of their musculotropic, heart-stimulating side effects, e.g., the non-dihydrogenated ergot alkaloids²⁹⁹⁴ and prisco-line²⁶¹, even though a normalizing influence of these drugs on the human electrocardiogram was reported in some instances^{1399, 2446, 2995, 2994, 2562, 2564}.

The dihydrogenated ergot alkaloids, especially CCK-170 (hydergin), are largely devoid of such disturbing musculotropic effects. They tend to diminish the abnormally large stroke volume and cardiac output of the "minute volume" hypertension^{299, 3454} and to normalize the hypoxic electrocardiogram^{299, 1701, 2515} mainly by action via the central nervous system^{1163, 1701, 2434}. However, these effects are hardly pronounced or persistent enough to produce striking changes in the clinical course of hypertensive heart disease.

The *veratrum* alkaloids activate vagal reflexes¹⁵⁴³ but do not markedly affect the cardiac output in hypertensive patients³⁶²⁶. Whether their long-range administration would offer advantages which might counterbalance their unpleasant side effects (p 304) appears doubtful.

Preliminary observations with the promising ganglionic blocking *penta- and hexamethonium salts*^{72 2610 3156} seem to indicate a tendency toward improvement of the electrocardiogram, a slight diminution of the heart size, reduction of breathlessness and pulmonary congestion, but apparently no distinct effect on fully developed cardiac failure. Anginal symptoms were provoked in some instances by a precipitous fall of the blood pressure which apparently caused a critical reduction of coronary flow³¹⁵⁶.

Much more strikingly beneficial effects on the electrocardiogram than those obtained by drug treatment have been achieved in large numbers of cases through the various techniques of *extensive sympathectomy*. Partial or complete normalization of pre-operatively pathological electrocardiograms, chiefly of the hypoxic, left ventricular "strain" type, was observed for periods of months to years in 57 to 78 per cent of several large series of patients^{155, 730, 1357, 2552, 3605} and in a number of smaller groups^{16, 173 246, 1515, 1821, 2495, 2910, 2945}. In less than 15 per cent of all cases, the electrocardiogram became worse after operation¹³⁵⁷. These results appear highly significant, since follow-ups of non-surgically treated hypertensive patients showed a gradual deterioration of the pathological electrocardiograms in the majority of instances, while spontaneous improvements occurred only as exceptional events^{83, 190, 463, 2909}. Lowering of the blood pressure is not a necessary prerequisite for normalization of the electrocardiogram, as mentioned on p 463 (Figs. 77, 78) and further below.

Significant decreases of the heart size after supradiaphragmatic or lumbo-

Because of the exceptional interest of these recent observations, the salient data will be presented here individually:

The patient whose case was published by Green and associates¹³², a 28-year-old woman, had complained of ankle edema, dyspnea and precordial pain, the electrocardiogram showed left heart strain. The roentgenographic area of the heart was 15 per cent above the upper normal limit. Unilateral adrenalectomy did not produce any improvement. Edema became even more marked. After removal of the second adrenal gland and under maintenance with adrenal cortical extract, the cardiac signs disappeared and the size of the heart became normal.

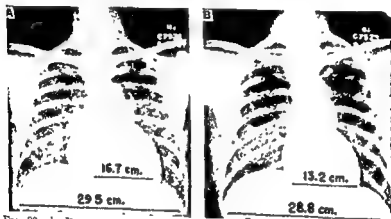


Fig. 80. 1. 75
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Among four of the 23 cases, published by Wolferth and co-workers¹³⁴, one, a 33-year-old woman, was freed from attacks of paroxysmal dyspnea by unilateral adrenalectomy, combined with thoracolumbar sympathectomy. Two others were subjected to subtotal adrenalectomy alone. Both have been completely relieved of severe congestive failure and do no longer require cardiac treatment. One is working full time as a barber. The fourth patient, a 57-year-old man, had not responded to the Peet sympathectomy and developed cardiac failure with severe edema.

... , an those who had displayed an enlargement of the heart showed a reduction of its size after the operation. Disappearance of dyspnea was reported in the cases of Zintel *et al.*¹³⁵.

T1 in 89 out of 310 hypertensive patients, treated with the rice diet for at least one month and for an average 10 months. In 30 out of 99 cases in which T1 had been completely inverted before treatment, it became upright. In 214 cases the electrocardiogram remained unchanged; in seven it became worse. The favorable results were in essence confirmed by others^{2510, 2513} after critical comparison with carefully observed control series²⁵¹³. Both Kempner¹⁷⁴⁴ and Watkin *et al.*²⁵¹³ emphasize that the improvements of the electrocardiogram show no direct relation to the response of the blood pressure level; in fact, that they may occur despite persistently unchanged hypertension.

The disappearance of the T-wave depression during sodium withdrawal seems to indicate an improvement of myocardial oxygen economy. Nothing definite is yet known concerning the influence of changes in the intra-extra-cellular electrolyte distribution upon the metabolic activity of the adreno-sympathogenic catecholamines, but the phenomenon of weakening of the pressor effects of both epinephrine and nor-epinephrine by salt withdrawal^{2703, 2707} suggests that the latter may possibly also modify their metabolic action on the myocardium. Another feature which may be of significance is the depression of nerve excitability and of the ability of nerves to conduct impulses in a state of sodium deficiency^{412a}.

The transverse heart diameter was found by Kempner¹⁷⁴³ to regress under the influence of the rice diet in 93 per cent of 286 hypertensive patients from an average 14.2 cm to an average 12.9 cm, while it expanded in the remaining 5 per cent (Fig. 75). This observation was confirmed by other workers^{2511, 2512}, including the writer and his associates²⁷¹³. Its significance is not quite clear since no accurate roentgenological differentiation can be made between diminishing dilatation and diminishing hypertrophy. Although the reduction in heart size was more conspicuous in the patients who displayed a significant fall of the diastolic pressure²⁵¹², there were also instances of marked diminution of the cardiac diameter in the face of a persistently high blood pressure¹⁷⁴³ (Fig. 80). It is possible that the reduction of the circulating plasma volume which results from a prolonged intake of the rice diet²⁴⁰⁸ may account for part of the changes in the heart size. However, the experimentally demonstrated importance of a high sodium intake for the production of cardiac hypertrophy by DCI^{2056, 3091, 3224a} and by the pituitary growth hormone or by combinations of the two³⁷⁹¹ makes it appear probable that sodium withdrawal would have the opposite effect.

Only few details have been published up to the present concerning the effects of subtotal or total bilateral adrenalectomy in severely hypertensive patients regarding their cardiac condition; but according to the reports on five cases in which congestive failure had existed pre-operatively, the signs of cardiac decompensation were completely abolished by the operation.

ence of unchanged high blood pressure levels, which proves their relative independence of the hemodynamic state prevailing in hypertension and the inadequacy of the mechanistic "burden" theory.

In agreement with the above-outlined pathogenic conception, the following therapeutic measures have been found effective concerning "hypertensive" heart disease, regardless of the behavior of the blood pressure (even though usually accompanied by its reduction): (a) sympathectomy, by elimination of a large portion of the neuro-secretory sources of cardiotoxic catecholamines; (b) sodium withdrawal, by elimination of the chemical mediator of cardiotoxic mineralocorticoid action; (c) bilateral adrenalectomy, by elimination of the intracellularly sodium-depositing mineralocorticoids and of adrenal medullary secretion; (d) thyroid inactivation, by elimination of the physiological potentiator of hypoxia-producing catecholamine action in the heart muscle.

Adrenalectomy must remain limited to desperate cases because of the risks of the operation and the inconvenience and expense of closely supervised permanent post-operative maintenance treatment with cortisone or cortical extracts. However, the fact alone of the results so far achieved, appears as an important landmark in the hesitant but inevitable progress of cardiology toward a close alliance with endocrinology.

The results of adrenalectomy do not yet reveal directly the nature of the underlying chemical process; but by virtue of their similarity with those obtained by sodium withdrawal, sympathectomy and thyroidectomy, they lend further strength to the view that hypertensive heart disease is the product of a complex neurohormonal and hormonal derangement in which the hypoxia-producing adrenosympathogenic catecholamines with the potentiating support of the thyroid hormone, of the sodium-accumulating mineralocorticoids and probably also of the hypertrophy-stimulating pituitary growth hormone, play the leading part.

Further applications of this concept to the problem of congestive heart failure in general will be discussed in a special section (p. 490 ff.).

Summary

It is becoming increasingly probable from many indications that so-called "hypertensive" heart disease, although frequently initiated by and co-existing with arterial hypertension, is not caused solely by the mechanical "load" of the high blood pressure but is essentially the result of neurohormonal and hormonal interferences in myocardial metabolism. These biochemical effects on the heart muscle seem to be closely related to those neurohormonal and hormonal influences which, by simultaneously acting on the arteriolar musculature as target tissue, give rise to hypertension.

It is conceivable that the struggle against increased peripheral resistance makes the heart muscle metabolically more susceptible to the effects of hypoxia-producing and hypertrophy-promoting neurohormones and hormones, namely: (a) the adrenosympathogenic catecholamines, whose oxygen-wasting activity is potentiated by the thyroid hormone, and (b) the adrenal mineralocorticoids which, jointly with the pituitary growth hormone, contribute to potential metabolic cardiac damage by promoting excessive myocardial cell growth (hypertrophy) and by upsetting the myocardial electrolyte balance (intracellular sodium accumulation and potassium loss).

An elevated peripheral resistance is not a necessary prerequisite for the development of the features of "hypertensive" heart disease, since all the anatomical, functional and electrocardiographic signs of "hypertensive" heart disease can (a) develop in the complete absence of hypertension and (b) disappear in hypertensive patients under treatment despite the persist-

contain an unstable and nondialyzable material which exerted a "digitalis-like" toxic effect on the isolated frog heart and showed some similarity of action with phenol and paracresol but was not chemically identified¹¹⁹. Highly toxic extracts from the blood of uremic patients were obtained by several workers^{12, 121}, including the writer¹²².

Symptomatology

The general symptomatology of advanced uremia^{123, 124} is characterized by a variety of nervous manifestations, such as drowsiness, apathy, psychotic reactions, headache, increased reflexes, muscular twitchings; furthermore, nausea and vomiting, bloody diarrheas, anemia, a yellowish-gray discoloration of the face, skin eruptions, stomatitis, and a deep, sighing respiration.

Unless signs of cardiac failure had existed before onset of the uremic syndrome, the advent of overt cardiac manifestations such as pulmonary congestion, dyspnea, palpitations, bloody sputum and particularly pulmonary edema^{72, 125, 126, 210} must be regarded as a grave development, foreshadowing the fatal outcome within a matter of weeks, as a rule¹²². Cardiac failure concerns mainly the left ventricle, but occasionally the signs of additional right ventricular failure supervene with the progress of the disease, leading to hepatic congestion, venous engorgement and marked peripheral edema. Gallop rhythm¹²² and pulsus alternans^{126, 127} are observed in some cases. Tachycardia is common but bradycardia may also occur occasionally^{129, 268}.

Serofibrinous pericarditis, producing friction rub, pain, and characteristic electrocardiographic changes^{122, 123, 216, 226}, constitutes perhaps the most specifically uremic cardiac manifestation in cases with renal excretory insufficiency.

Abnormalities of the electrocardiogram are almost invariably present in the advanced stages of uremia. In some cases they are caused by pre-existing hypertensive heart disease and/or coronary sclerosis. They may be complicated by the superimposed effects of uremic pericarditis (concordant elevations of S-T)^{226, 228} and by changes in the electrolyte balance, such as hypocalcemia (prolonged Q-T)^{122, 123} and hyperpotassemia (tall, peaked T-waves^{127, 128, 228, 229, 263}, tendency to disappearance of P_{123, 232, 270 and preterminal intraventricular block²²¹).}

Electrocardiographic changes of the hypoxic type (flattened or inverted T in one or more leads, depression of S-T) are very commonly present in uremia^{122, 123, 128, 129, 226, 229, 270} and are usually ascribed to the "strain" of co-existing hypertension or to coronary sclerosis¹²³ rather than to the uremic state itself. However, it seems worthy of note that such changes are also seen in mildly hypertensive or normotensive uremic indi-

The Heart in Uremia

Definition and General Principles

The clinical picture of uremia presents so many impressive though variable symptoms on the part of the central nervous system, gastrointestinal and respiratory tracts, hematopoietic apparatus, eyes and skin, that comparatively little attention is being paid in general to the frequently co-existing cardiac disturbances, and to the fact that death in uremia is in a large number, indeed probably in the majority of cases, precipitated by cardiac failure.

A causal connection of cardiac complications with the uremic state *per se* may not appear particularly conspicuous in patients with hypertension of long standing and in elderly persons, suffering from pyelonephritis, and the like. The comparative rarity of serious cardiac lesions in the pre-uremic course of subacute and chronic glomerulonephritis²⁷⁹⁷ and polycystic kidney, etc., on the other hand, adds pathogenic significance to the more or less simultaneous appearance of uremic manifestations and of ominous electrocardiographic signs in these latter conditions.

In any instance of uremia occurring in connection with impaired urinary excretion, including lower nephron nephrosis and obstructive processes, it appears logical to suspect retained waste products as contributing significantly to the origin of whatever cardiac signs may make their appearance. Beyond this generality, however, no unanimity has yet been reached as to which substance or combination of substances has to be made responsible for the development of cardiac disturbances in uremia.

The characteristically cardiotoxic effects of hyperpotassemia stand apart, insofar as toxic accumulations of potassium occur only in a minority (about 20 per cent) of cases^{1730 1732 1915 3277} and, as a rule, only in the terminal stage for a few days, rarely for periods of weeks¹⁹¹⁵ before death.

If and when the serum potassium concentration approaches the level of 10 mEq per liter, danger to life becomes imminent and ensuing death has to be regarded as being caused primarily by potassium action which elicits ventricular fibrillation or standstill, according to experimental^{1437 2420 3553} and clinical^{1730 1731 1912 2215 3352} experience.

In the great majority of instances of beginning, advanced and finally fatal cardiac failure in uremic patients, other factors than potassium must be involved. None of the better-known retained metabolites, such as urea, creatinin, phenols and guanidine (lit., see ^{361 2475}), could be tracked down as specific offenders. The serum of uremic dogs and humans was found to

contain an unstable and nondialyzable material which exerted a "digitalis-like" toxic effect on the isolated frog heart and showed some similarity of action with phenol and paracresol but was not chemically identified¹¹⁹. Highly toxic extracts from the blood of uremic patients were obtained by several workers^{121, 122}, including the writer¹²³.

Symptomatology

The general symptomatology of advanced uremia^{124, 125} is characterized by a variety of nervous manifestations, such as drowsiness, apathy, psychotic reactions, headache, increased reflexes, muscular twitchings; furthermore, nausea and vomiting, bloody diarrheas, anemia, a yellowish-gray discoloration of the face, skin eruptions, stomatitis, and a deep, sighing respiration.

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etc.

ST. A common cardiac manifestation in cases with renal excretory insufficiency

Abnormalities of the electrocardiogram are almost invariably present in the advanced stages of uremia. In some cases they are caused by pre-existing hypertensive heart disease and/or coronary sclerosis. They may be complicated by the superimposed effects of uremic pericarditis (concordant elevations of S-T)^{136, 137} and by changes in the electrolyte balance, such as hypocalcemia (prolonged Q-T)^{138, 139} and hyperpotassemia (tall, peaked T-waves^{140, 141, 142, 143, 144}, tendency to disappearance of P^{145, 146, 147} and preterminal intraventricular block¹⁴⁸).

Electrocardiographic changes of the hypoxic type (flattened or inverted T in one or more leads, depression of S-T) are very commonly present in uremia^{149, 150, 151, 152, 153, 154, 155, 156, 157, 158} and are usually ascribed to the "strain" of co-existing hypertension or to coronary sclerosis¹⁵⁹ rather than to the uremic state itself. However, it seems worthy of note that such changes are also seen in mildly hypertensive or normotensive uremic indi-

viduals (e g, in cases of obstructive pyelonephritis or polycystic kidney²⁶⁷⁵) and that in some cases the hypoxic changes become more marked with the progression of uremia²⁶⁷⁶. In bilaterally nephrectomized dogs, typical hypoxic alterations of the electrocardiogram appeared within a few days without significant changes of the blood pressure^{1299*, 2930}. These latter observations suggest that the hypoxic electrocardiogram in uremia is more intimately connected with the uremic state per se than is generally realized. The presumably neurohormonal mechanism of its origin will be discussed below.

Pathology

Opinions regarding morphological cardiac pathology in uremia are divided. The histological lesions of the myocardium, which are found in many cases, were interpreted by some workers as displaying certain characteristics, specific for severe renal diseases and uremia^{1226, 2109}, while others^{1915, 2935, 2193} question the specificity of these changes and consider them as identical with those pertaining to hypertensive and arteriosclerotic heart disease. Frequently the heart appears hypertrophied, pale, mottled yellow or gray and of poor consistence. Fatty degeneration, possibly caused by anemia, is often present; multiple necrotic foci and cloudy swelling of the myocardial fibers, interstitial edema and myocarditis were reported as typical findings^{1226, 1915, 2114, 2199}. Usually these lesions are most pronounced in cases of renal arteriolar sclerosis and pyelonephritis and less conspicuous in those with chronic glomerulonephritis²¹⁹⁹. Endothelial hyperplasia of the cardiac arterioles was seen in conjunction with necrotizing arteriolitis of the kidneys²¹⁹⁹. Acute or chronic fibrinous pericarditis is encountered post-mortem in 20–40 per cent of uremic cases. It is in most instances accompanied by degenerative myocardial lesions^{1226, 1915}.

The creatine content of the uremic heart muscle was found augmented by some workers^{2049, 2062}, while others¹³⁰² reported opposite results.

Neurohormonal and Hormonal Aspects

In 1939, Agnoli and Bussa¹⁵ showed that the intraperitoneal or intravenous injection of crude uremic serum or of dialyzates from uremic serum into guinea pigs produces marked electrocardiographic changes and eventually death. The nature of the toxic material involved remained obscure.

Subsequently (1944), the writer made the colorimetric observation^{2676, 2692} that the serum of patients in advanced uremia contains regularly excessively large amounts of catecholamines (Fig. 81). In contrast to normal serum and to that of non-uremic hypertensive individuals, the serum of uremic patients produced strikingly stimulating effects on the isolated frog heart (Fig. 82), sometimes alternating with periods of cardiac standstill. Protein-

free extracts, made from uremic serum, proved highly toxic in rabbits. They caused flattening or inversion of the T-wave, depression of S-T, tachycardia or bradycardia and death within eight to 22 minutes (Fig. 83).

Abnormal electrocardiograms of the epinephrine-like, hypoxic type (flat or inverted T, depressed S-T) were obtained in 22 out of 25 uremic patients

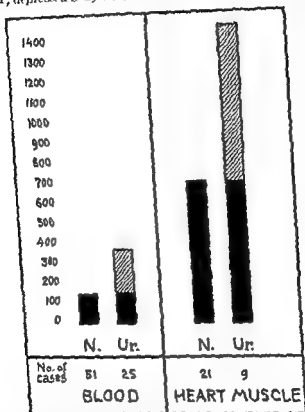


Fig. 81 Average catecholamine concentrations in the blood and heart muscle of normal individuals and uremic patients. (Excess catecholamines shaded)
(After W. Rash, *J. Lab. & Clin. Med.* 29: 715, 1944)

whose blood catecholamines were abnormally high. Only two uremic patients presented normal catecholamine concentrations. Their electrocardiograms were normal. In three repeatedly examined cases, the T-wave changes became more accentuated as the catecholamine level rose. In one case, the T-wave

was well above the upper limit of "normal" (Fig. 84), i.e. of the readings, obtained in 21 hearts from patients who had died from non-cardiac conditions.

From these findings the conclusion was drawn that the presence of excess amounts of catecholamines of probably adrenosympathetic origin (epinephrine and related substances) in the blood and heart muscle constitutes a characteristic feature of uremia and that these catecholamines participate significantly in the chemical mechanism which leads to cardiac failure and death in such cases^{267*}. While this concept needs further consolidation by chromatographic and biological tests which are in progress at this time, there are several further facts which seem to support it:

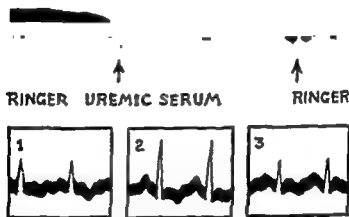


FIG 82 Epinephrine-like effect of uremic serum on the contraction amplitude of the isolated frog heart. Electrocardiogram of the patient whose serum was used. Blood pressure was 224/120, NPN 123 mg per cent, catecholamines 475 color units per cc

(Re drawing after W. Rarb, J. Lab. & Clin. Med. 29: 715, 1944)

(a) Positive benzodioxane and regitine tests which specifically indicate circulating epinephrine¹¹⁵² were obtained in several cases of uremia¹¹⁷⁵ 1253 2604 2692 2573 (Fig. 85, 86), in one of these cases hyperadrenalinemia was ascertained also by fluorimetry¹¹⁶⁰,

(b) The non-response of the blood pressure of uremic patients to the otherwise depressant ganglionic blocking tetraethylammonium was suspected as being due to circulating epinephrine, because it had been found that tetraethylammonium, by virtue of its locus of action, fails to overcome the pressor effect of injected epinephrine¹¹¹¹,

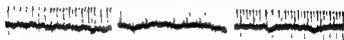
(c) Hemodynamic studies in cases of renal hypertension showed that their slightly subnormal cardiac output and their markedly increased peripheral resistance give way to an increase of the cardiac output and to a

diminution of peripheral resistance when renal excretory insufficiency sets in¹⁴², thus, a hemodynamic situation arises in uremia which corresponds to the characteristics of epinephrine action.

(d) In experimental uremia, the terminal stage is accompanied by hypoxic electrocardiographic changes of the epinephrine type (flat or inverted

RABBIT.-I.V. INJ. OF ALCOHOLIC EXTRACTS OF BLOOD SERA

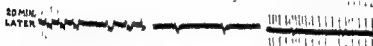
BEFORE INJECTION:



NORMAL SERUM (EXTRACT OF 10 cc.):



UREMIC SERUM* (EXTRACT OF 10 cc.):



* of 34 yrs. - BLOOD AC 305 cal. un/cc, NPN 172 mg%, BLP. 215/130 mm.



FIG. 83. Continued.

(after W. Haah, *J. Lab. & Clin. Med.* 29: 715, 1944)

T, depressed S-T)^{129a, 292b}, unless hyperpotassemia interferes¹⁴⁷; tachycardia develops at the same time and tends to terminate in ventricular fibrillation and death²⁸⁸.

(e) The urinary excretion of "uro-sympathin" was found diminished in cases of severe renal lesions^{154, 156} and recent colorimetric studies of the writer in collaboration with W. Gigue²⁹⁷ are likewise suggestive of a disproportionately low urinary excretion of catecholamines by uremic patients. It appears probable, therefore, that the accumulation of cardiotoxic

catecholamines in the uremic blood is due to abnormal retention as a sequel of renal excretory insufficiency, since circulating adrenosympathogenic catecholamines are normally eliminated by the kidneys, largely in an inactive conjugated form, accompanied by small amounts of free active epinephrine and nor-epinephrine^{252, 475, 862, 911, 946, 1151, 1450, 2794}.

The terminal hyperpotassemia in uremic animals and humans is caused

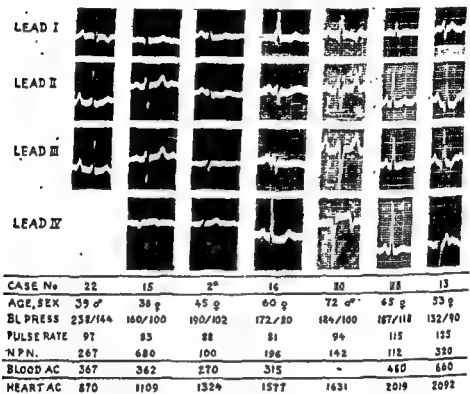


FIG 84 Electrocardiograms of uremic patients with high catecholamine concentrations in blood and myocardium ("AC" stands for "Adsorbable Catecholamines")

(After W Raab, J Lab & Clin Med 20 715, 1944)

essentially by retention during prolonged oliguria and anuria¹²³⁷. Nevertheless, the possibility must not be disregarded that part of the circulating excess potassium may have been shifted from the cells into the extracellular fluid. This is suggested by some case reports according to which hyperpotassemia developed in the absence of complete urinary suppression^{979, 1229, 1731} and by the variability of the serum potassium level, regardless of potassium intake¹⁷³². Since epinephrine and nor-epinephrine mobilize potassium from the tissues¹⁹⁶², especially from the liver⁴⁰⁰ into the circulation, it appears possible that the elevation of the catecholamine (epinephrine²)

level in the uremic blood may act as a contributory factor in the origin of hyperpotassemia.

Observations, indicating a beneficial and life-prolonging effect of DCA and testosterone administration in nephrectomized uremic animals^{221, 222, 223, 224, 225, 226, 227}, were not²²⁸ or only partially²²⁹ confirmed by other workers. The mechanism of action of these steroids in uremia remains to be elucidated.

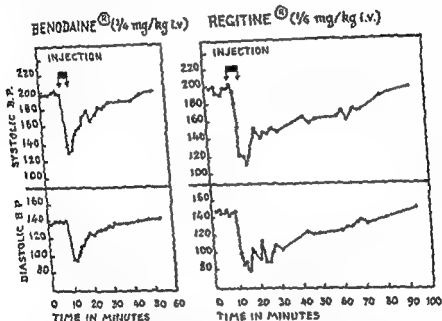


FIG. 85 "Positive" benzodioxane and regitine reactions of the blood pressure in a uremic patient without pheochromocytoma, suggesting the presence of excess epinephrine in the circulating blood.

(Re-drawing after J. R. Lambet, K. S. Grimson, D. M. Bell and E. S. Organ, J. A. M. A. 146: 1353, 1951)

Treatment

The therapeutic attempts directed against the uremic syndrome as a whole and against those of its etiologic factors, which are potentially curable, such as obstructions and infections of the urinary tract, need not be discussed within the framework of this review on endocrine and neurogenic pathogenic mechanisms. Since such mechanisms have never been considered by other clinical workers as participating in the uremic syndrome and in particular in the origin of its cardiac complications, no specific efforts have yet been made to treat the uremic heart from this point of view.

It should be mentioned, however, that certain therapeutic methods which

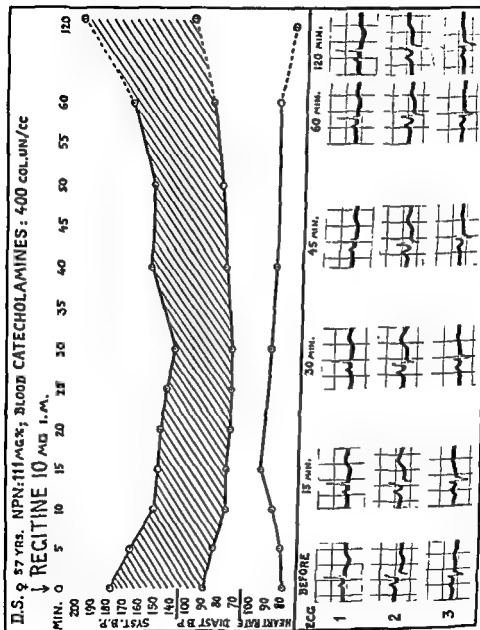


FIG 80 Positive regitine test in a case of Kimmelstiel-Wilson syndrome with uremia. Note elevation of T1 and T2 during action of the drug.
 (After W. Raab and S. J. Yaffe, unpubl.)

gave partly satisfactory results, at least in cases of acute and reversible renal insufficiency, such as external blood dialysis with artificial kidneys^{141, 207} and peritoneal lavage²⁴⁵, may be assumed to exert possibly their beneficial effects by eliminating together with other toxic material also a substantial portion of the circulating accumulated catecholamines.

In view of the colorimetric and biological findings which suggest the presence of abnormally large quantities of adreno-sympathogenic catecholamines in the blood, and considering the reports of positive adrenolytic tests in uremic patients (see preceding section), the tentative therapeutic application of long-acting adrenolytic drugs, especially of the new β -haloalkylamines, seems theoretically justified and is being studied at the present time by the writer.

Summary

Electrocardiographic signs of myocardial hypoxia, and ultimate congestive cardiac failure develop in most cases of advanced uremia. Diffuse degenerative and necrotic changes and fibrinous pericarditis are frequently found post-mortem. Except in instances of pre-existing severe heart disease, these cardiac manifestations are, in all likelihood, elicited by some retained substances circulating in the uremic blood. One of these is potassium, which accumulates in the blood in toxic and potentially fatal concentrations in about 20 per cent of the cases, but only in the terminal stage.

A heretofore disregarded, almost invariable finding in the blood of patients with advanced uremia is the presence of highly increased amounts of cardiotoxic catecholamines of probably adreno-sympathogenic origin (epinephrine and related compounds).

The following observations in uremic patients seem consistent with a presumable renal retention of catecholamines which are otherwise excreted by the normal kidney. (a) positive benzodioxane and regitine tests, (b) failure of tetraethylammonium to depress the blood pressure; (c) low urinary catecholamine excretion, (d) hemodynamic and electrocardiographic alterations, analogous to those produced by epinephrine; (e) degenerative myocardial lesions, similar to those produced by epinephrine, (f) excessive catecholamine concentrations in the heart muscle.

These latter findings suggest a decisive role of retained catecholamines in the ultimately fatal cardiac complications of uremia.

Congestive Heart Failure

Definition and General Principles

In speaking of "congestive heart failure", we do not refer to a pathogenically clearly defined clinical entity with a definite etiology and a sharply circumscribed uniform symptomatic pattern; but rather to a fluctuant array of cardiovascular and resulting respiratory, renal, cerebral and other manifestations, all of which revolve around the central feature of a reduction of cardiac output relative to inflow.

According to the exclusive or prevalent location of this kind of disturbance in the left or right half of the heart, one applies the terms left or right-sided failure respectively, but in many cases both of these alternatives merge into the syndrome of bilateral heart failure.

Since the classical description by Hope¹⁸⁶¹ in 1842, the symptomatology of congestive heart failure has been the subject of numerous treatises and its details do not need to be repeated here except for a brief enumeration of the principal signs and symptoms as they appear in typical cases. An interpretation of their general and individual pathogenic background with particular consideration of neurohormonal and hormonal factors will be attempted subsequently.

Pure left-sided failure is characterized primarily by manifestations of pulmonary congestion due to the inability either of the left auricle (as in mitral stenosis) or of the left ventricle (as in left ventricular or aortic lesions) to expel the full equivalent of pulmonary venous inflow into the left ventricle or into the peripheral circulation respectively. The resultant damming back of blood in the pulmonary vessels gives rise to congestive phenomena such as dyspnea on exertion, or in more advanced stages also at rest. The latter occurs especially in the recumbent position (orthopnea) and during the night, often in paroxysmal attacks without or with pulmonary edema, Cheyne-Stokes type of respiration, cough, blood-tinged sputum and moist râles over the lung bases. The vital capacity diminishes and fluid accumulates in the pleural cavity. Radiographic changes indicate pulmonary vascular engorgement, diffuse flooding of the alveoli and fluid in the pleural spaces, the latter usually more marked in the right half of the chest. The pulmonary circulation is slowed down as evidenced by a prolongation of the "arm-to-tongue" test with decholin or saccharin beyond the normal time of 9-16 seconds.

Pure right-sided failure (as in pulmonary fibrosis and other diseases of the lungs, stenosis or sclerosis of the pulmonary arteries, Bernheim's syn-

drome, tricuspid anomalies) occurs much less frequently than pure left-sided failure. Its clinical symptoms are essentially attributable to engorgement of the systemic veins and capillaries and to the functional alterations arising in the congested kidneys, brain, and liver, combined with apparent hormonal derangements which will be discussed later (p. 490 ff.). Sodium and water retention (p. 496 ff.) augment the circulatory volume. This aggravates the disproportion between venous inflow and cardiac output; and together with the increased hydrostatic pressure in veins and capillaries, it promotes the formation of peripheral edema and ascites. The liver is enlarged; in the acute phase of congestion it is tender to pressure or even spontaneously painful. Slight jaundice appears occasionally. General weakness, cyanosis of skin and mucous membranes, prominence of the veins, of the neck, a positive hepato-jugular reflux test (visible swelling of the neck veins during manual compression of the liver), an increase of the venous pressure above 10 cm water and an "arm-to-lung" time (ether) of more than eight seconds, indicating an abnormally slow systemic circulation, complete the picture. The urine output is low, with a high specific gravity, albuminuria and often increased urobilinogen. Cerebral edema may be manifested by headaches, depression and psychotic states.

While pure, primary right-sided failure is a comparatively uncommon occurrence, there are numerous instances in which a combined bilateral failure results from an originally left-sided ventricular or auricular decompensation, which had raised the intrapulmonary pressure to the point of incompatibility with continued adequate emptying of the thin-walled right ventricle against the abnormally elevated resistance. Congestion in the systemic veins and capillaries adds the features of right ventricular failure to those of left-sided decompensation.

Developments of this kind are common in cases of aortic regurgitation, aortic stenosis and mitral stenosis. Furthermore, they occur with great frequency in so-called "hypertensive" and arteriosclerotic heart disease, but in these latter conditions one has to reckon from the beginning with the probability of a more diffuse, bilateral myocardial involvement. This is particularly true in those instances in which coronary sclerosis affects both ventricles or in which a general neurohormonal and endocrine interference in myocardial metabolism forms the background for both left and right ventricular failure. More or less diffuse myocardial metabolic anomalies seem to pave the way for the development of bilateral failure also in other conditions, such as idiopathic cardiac hypertrophy, beri-beri, infectious pancarditis, severe chronic anemia, and prolonged paroxysmal tachycardia.

The question as to whether the clinical features of congestive heart failure should be attributed mainly to "forward" failure^{254, 255}, i.e., diminished arterial (forward) output, or to "backward" failure^{256, 257}, i.e., congestive

tion of blood in the great veins and capillaries, is still a matter of argument. In recent years interest has been focused on the more specific application of these two concepts to the behavior of renal blood flow and to the role of the latter in the salt and water retention which produces hypervolemia.

Proponents of the "forward" hypothesis^{2315, 2316, 2364, 2344} maintain that the phenomenon of hypervolemia is essentially attributable to the decrease of renal blood flow, caused by low cardiac output, and to a resulting reduction of filtration rate; while those who favor the "backward" hypothesis^{234, 274, 2097} ascribe the sodium and water retention to elevated venous pressure in the kidneys. In view of the fact that neither of both concepts is entirely consistent with all clinical observations, but that both are well supported to a certain extent, attempts have been made to reconcile the opposite opinions by the assumption that both mechanisms operate simultaneously, even though in individually varying degrees^{265, 1060, 2792}.

Pathology

There is no single type of gross anatomical anomaly of the heart which would constitute an obligatory prerequisite for the development of congestive failure. Of course, valvular lesions and congenital malformations, which expose certain sections of the heart to abnormal internal pressure by obstruction of their outflow (stenoses) or by an abnormally increased inflow (regurgitations), can produce dilatation and dynamic failure of the respective ventricle or auricle which may or may not be followed by secondary failure of other parts of the heart, situated in upstream direction. Internal mechanical encroachments on ventricular or auricular cavities, as in cases of Bernheim's syndrome, cardiac tumors, large thrombi, and the like, are rare events of minor practical significance.

The fact that those cardiac chambers which are placed under greatest mechanical strain are the first to display hypertrophy and dilatation, and the first to fail functionally, confirms the rule that *myocardial hypertrophy is usually (though not necessarily) initiated by increased distention and work*^{1033, 1014} and in apparent proportionality to the increase of local metabolism³⁰²². The latter rises according to Starling's "law of the heart"¹²²⁹ which retains its general validity, although its quantitative aspects are derived from experiments on the denervated heart and do not fully apply to conditions of the heart in situ which is subjected to divergent nervous influences upon myocardial oxygen consumption²⁰⁵². The presumable involvement of hormones in the process of cardiac hypertrophy has been discussed on p. 461 ff. It concerns especially the growth hormone of the pituitary, without whose participation mechanical strain is incapable of producing myocardial hypertrophy.

In those numerous instances in which no mechanical defects of the heart

and of its valves exist and in which no increased peripheral arterial resistance (hypertension, coarctation of the aorta, pulmonary disease) or increased venous return (arteriovenous shunt) had put one or more chambers of the heart under strain, the primary causes of cardiac failure are to be sought in the myocardium itself. Marked coronary sclerosis with extensive fresh or healed myocardial infarctions, as well as inflammatory changes, such as rheumatic pancarditis and other types of infectious myocarditis, or the pathogenically obscure Fiedler's myocarditis, can give rise to congestive failure. However, the correlation between such morphologically identifiable myocardial lesions and the occurrence or degree of cardiac failure is not a regular one, in that quite marked histological changes may be found in the hearts of persons who had not shown any signs of congestive failure and vice versa.

The same applies to fatty or hydropic degeneration, necrosis and fibrotic foci which, although frequently observed in failing hearts, are too unspecific and too irregular in occurrence to be made responsible by themselves for the phenomenon of dynamic myocardial failure²⁸, even though they do indicate that chemical forces, detrimental to myocardial integrity, have been at work during life.

Since lack of oxygen is generally believed to constitute a particularly important element in the metabolic mechanism of cardiac failure, much emphasis has been placed upon a presumable impairment of oxygen supply to the individual myocardial cell of the hypertrophic heart. Both the slowness of oxygen penetration into the interior of the thickened muscle fibers^{42, 137} and an insufficient number of myocardial capillaries relative to the increased myocardial mass^{136, 211}, are being accused as hypoxia-producing factors which result from cardiac hypertrophy per se. The validity of these concepts has been questioned²⁹, however, and chemical interferences in the oxygen economy of the failing heart muscle must be taken into consideration. They will be discussed in the following section.

Enlargement of the failing heart

gestive

Thus passive congestion, as contrasted with the "tonogenic" functional dilatation of the athlete's heart (p. 449) and of early hypertensive heart disease (p. 458), develops parallel with a reduction of the energetic functional reserve of the metabolically damaged myocardium (see below). It is accompanied by an increasingly wasteful oxygen consumption relative to the amount of work performed^{140, 211, 214, 220}. Ventricular hypertrophy, by its hypothetical impairment of oxygen uptake and utilization, by its interference jointly to an ultimate limit of the respective cardiac

There are no specific morphological criteria which would distinguish the degenerative myocardial lesions, found in failing hearts in various endocrine syndromes, such as pheochromocytoma (p. 87), hyperadrenocorticism, thyrotoxicosis (p. 141), acromegaly (p. 168), and those, connected with an excessive accumulation of catecholamines in the heart muscle (beri-beri, uremia), from the ones seen in "hypertensive" heart disease (p. 460) and "idiopathic" cardiac hypertrophy (p. 444). The characteristic features of these degenerative lesions can be experimentally produced by the administration of certain hormonal agents, namely epinephrine (p. 18), thyroxin (p. 40), and desoxycorticosterone acetate (p. 32). Since these hormones as well as some of their natural homologues (nor-epinephrine, adrenal mineralocorticoids) are functionally intimately related with each other, it appears probable that they contribute jointly, though in varying quantitative combinations, to the establishment of the degenerative myocardial changes in question.

Neurohormonal and Hormonal Aspects of Myocardial Metabolism

Before entering into a discussion of the possible involvement of neurohormones and hormones in those anomalies of myocardial metabolism, which have been ascertained in failing hearts and to which a causal role in the development of congestive heart failure has been ascribed, it seems appropriate to point out briefly the most important phases of cardiac energy metabolism.

Glucose, which is taken up by the myocardium from the coronary circulation as the main substrate for *energy formation*, is completely oxidized to water and carbon dioxide after previous fission into two molecules of pyruvic acid. Under anaerobic conditions, however, this oxidative process cannot take place and pyruvate is reduced to lactate which may exert toxic effects on the heart muscle unless an adequate oxygen supply is quickly restored. Thiamine acts as coenzyme in the oxidation of pyruvic acid. Other coenzymes, which participate in the aerobic energy production of the heart, are likewise derivatives of the vitamin B complex. Following oxidative dehydrogenation, the hydrogen atoms of the substrate pass through a series of enzymatic carriers. In this process, energy is gradually released and converted into the energy of certain organic phosphate bonds which serve as temporary energy stores. Creatine and adenylic acid combine with some of these high energy phosphate groups to become phospho-creatine (phosphagen) and adenosine triphosphate (ATP) respectively. The latter represents the immediate source of energy for muscular contraction while the former provides energy reserves which can be enzymatically transferred to ATP. By means of the energy derived from ATP, certain muscular

protein molecules (actomyosin)^{1239, 1240} are believed to assume a shortened shape whereby energy is liberated as mechanical work and heat^{1239, 1240}.

A detailed discussion of normal myocardial metabolism and of its derangements in congestive failure was published in 1951 by Olson and Schwartz¹²⁷⁶. These authors list the following factors which might impair cardiac energy production: (a) oxygen lack, (b) enzyme or coenzyme lack, (c) hormonal lack or imbalance, (d) substrate lack. They quote the beri-beri heart as the best-known example of coenzyme deficiency. It will be recalled that evidence has been adduced, indicating an exaggerated accumulation of epinephrine in the myocardium in beri-beri (p. 438 ff.). Epinephrine in abnormal amounts produces marked myocardial hypoxia through excessive and energetically uneconomical oxygen consumption (p. 11 ff.) Hence, it appears probable that in the origin of cardiac failure in beri-beri, the element of relative oxygen lack may be of equal importance as the lack of coenzyme-lase.

Similar conditions may be assumed to prevail in the uremic heart with its abnormally increased catecholamine concentrations (p. 470).

A similar reasoning applies to the occasional development of congestive failure in thyrotoxicosis to which both a potentiated epinephrine action and a certain degree of thiamine deficiency seem to contribute their respective pathogenic share (p. 135). In experimental thyrotoxicosis, essentially the same metabolic alterations were found in the heart muscle as those elicited by epinephrine, namely excessive oxygen consumption, loss of creatine phosphate and of adenosine triphosphate, accompanied by an accumulation of lactic acid (p. 13 and p. 35). It appears logical to assume that the deficiency in energy supplying phosphate bonds is a significant factor in the ultimate reduction of cardiac work capacity¹²⁷⁶ which may lead to congestive failure.

No direct evidence is yet at hand which would prove that an exaggerated activity of the *hypoxia-producing adenosympathogenic catecholamines* (epinephrine and nor-epinephrine) is prominently involved in the origin of the common forms of congestive heart failure. However, the symptomatic, hemodynamic and myocardial morphological features of cardiac failure in cases of pheochromocytoma, "hypertensive" heart disease, beri-beri, uremic heart failure, etc., suggest an unduly intense local action of sympathomimetic catecholamines as a common pathogenic factor.

1239, 1240 and of phosphorus^{1239, 1240} in failing human hearts seems to be consistent with the writer's observation of abnormally high catecholamine

concentrations in the majority of the hearts from persons who had died in cardiac failure³⁷⁰.

Thus, the hypothesis is being advanced that abnormally increased adrenosympathogenic hypoxiating catecholamines play an important, though not necessarily primary, part in those derangements of myocardial metabolism which lead ultimately to congestive failure, at least in those cardiac syndromes in which an intensified sympathetic neurosecretory activity (neurogenic hypertension) or catecholamine retention (uremia) or catecholamine effect potentiation (thyrotoxicosis) can be assumed for good reasons.

Certain findings, obtained in failing denervated animal hearts (heart-lung preparation) which revealed normal amounts of ATP and increased amounts of phospho-creatine³⁷⁰, may be attributable to the fact that the above-described neurohormonal and hormonal interferences were prevented from participating in this experimental arrangement which differs fundamentally from clinical conditions by eliminating the sources of hormone and neurohormone influx into the heart muscle.

Investigations which were carried out in patients with congestive heart failure by means of cardiac catheterization, yielded contradictory results insofar as Goodale and co-workers¹³⁰² observed an increased oxygen extraction from the coronary blood, while the myocardial oxygen consumption was found normal by Bing and his associates³⁸¹. Both teams of workers agree, however, in view of the low cardiac output noted in their subjects, that the heart muscle was unable to convert oxidative energy efficiently into mechanical work. In other words, their findings prove that in the failing human heart a disturbance exists which may be identical with the characteristic myocardial oxygen wastage under the influence of the sympathomimetic catecholamines (p. 11 ff.). The absence of a more impressive absolute increase of oxygen consumption by these enlarged hearts may perhaps be explained on the grounds of the widely accepted contention that adequate oxygen uptake by the hypertrophic heart is hampered by the thickness of the muscle fibers and by a disproportion between myocardial mass and density of the capillary network. In consideration of this latter eventuality, a seemingly normal oxygen extraction by a failing enlarged heart may still be interpreted as being relatively high.

It seems worthy of note that some of the patients, examined by the above-named workers, were suffering from congestive heart disease due to valvular lesions, thus from conditions in which a primary increase of adreno-sympathetic neurosecretion has not yet been proven or been made probable by any specific investigations. Yet, the type of metabolic disturbance present, namely uneconomical oxygen wastage, corresponds to the typical effect of the sympathomimetic catecholamines, whether they be present in abso-

lately excessive amounts or merely abnormally effective, e.g., due to a deficiency of the oxygen-sparing vagal counterbalance. Further studies of the role of cardiac neurosecretory activity and of the adrenergic cholinergic equilibrium in the metabolic and dynamic response of the heart to valvular anomalies are needed.

A comparison of the clinical reaction of the heart to aortic stenosis on one hand with that to arterial hypertension on the other, both of which force the left ventricle to expel its contents against an increased resistance, shows certain significant differences. The heart rate in aortic stenosis is usually slow²⁹², that in essential hypertension is normal or accelerated. In aortic stenosis, congestive failure develops late, if at all, despite often marked left ventricular hypertrophy²⁹³. In hypertensive individuals, the tendency of the heart to become decompensated is much more prominent. Thus, it seems that under a similar dynamic strain, the "hypertensive" heart is more likely to fail because of a more inflexible myocardium in pathogenic neur

From the facts and concepts so far presented, it becomes apparent that the presumable participation of neurohormonal factors in the origin of the myocardial metabolic changes of congestive failure, although probably com-

Derangements of the myocardial electrolyte distribution are presumably of no lesser significance for the development and maintenance of congestive failure than those of the oxidative energy production. In this domain, the adrenal corticoids play a prominent part. Desoxycorticosterone, as the synthetic representative of the mineralocorticoids, has been shown to augment intracellular sodium in the heart muscle²⁴¹ and to deplete cardiac cell potassium²⁴¹. It is well known that an over-dosage of DCA

elicits all the manifestations of congestive heart failure if accompanied by a sufficient amount of sodium retention. In Addison's disease (p 98 and p 120). Congestive heart failure is a common complication of Cushing's syndrome (hyperadrenocorticism) (p 98), of toxemia of pregnancy (p 203), and of essential hypertension in which adrenal cortical over-activity is assumed to frequently participate (p 468). Conversely, congestive failure never occurs in Addison's disease. Spectacular improvements of cardiac decompensation have been achieved by adrenalectomy (p 509) and by withdrawal of sodium, the apparent chemical mediator of the injurious effects produced by the mineralocorticoids on the myocardium.

The heart muscle of persons who had died from congestive failure was found to contain abnormally high concentrations of sodium³⁶²⁴, while potassium was diminished^{2201, 2623} (see also p. 513), in analogy to the effects produced by an excess of mineralocorticoids^{664, 666, 2920, 3641a} and in contrast to the opposite electrolyte situation which prevails in the myocardium in the state of adrenal insufficiency²⁴²⁰. The myocardial water was unaltered (p. 513).

An increased mineralocorticoid activity in congestive failure is also suggested by renal retention of sodium (p. 499) and by the low sodium concentration which was observed in the thermal sweat^{1504, 2316} (though not without exception^{2747a}) and in the saliva³⁵⁴⁴ of patients with cardiac decompensation. Both the sweat and saliva tests are regarded as specific criteria of mineralocorticoid activity^{371, 2067, 2316, 3534}. The urine of edematous patients in congestive failure was found to contain abnormally high quantities of a sodium-retaining material¹⁷ and the plasma of some cases displayed increased adrenocorticotrophic effectiveness³⁴⁷.

While the above-listed observations suggest an increased mineralocorticoid activity as an important factor in at least a substantial number of cases of congestive heart failure, there exists also a report concerning an increased excretion of total corticoids and of glucocorticoids in some such cases²⁵³². These latter findings were interpreted as a secondary rather than as a causal phenomenon in heart failure. Both an increased glucocorticoid production as a result of the stress situation of general hypoxia^{766, 1920, 2010} and a diminished inactivation of corticoids by the congested liver may be considered as possible causes of their appearance in the urine in augmented quantities²⁵³². It must be mentioned, however, that in another series of observations in patients with congestive heart failure^{1923, 1926}, the urinary excretion of 11-oxysteroids and also of 17-ketosteroids was found below normal. The fact that the readings rose markedly during mercurial diuresis¹⁹ suggests the possibility of renal retention as the cause of the low urinary output of the above named adrenal steroids in these cases^{1923, 1926}. As far as hepatic inactivation of corticoids is concerned, this has been made probable for both DCA^{445, 1245} and glucocorticoids⁶⁹⁷. Its theoretically possible impairment by congestive changes of the liver may contribute to a further increased sodium-retaining mineralocorticoid activity in established congestive failure beside the problematic primary augmentation of mineralocorticoid formation.

Morphological studies²⁰³⁵ revealed in compensated cardiac individuals an increase of the weight and lipid content of the adrenal cortex, while the adrenals of those who had died in congestive failure showed a diminution of the cortex weight as well as of total cortical lipids and cholesterol esters. The last-named changes were regarded as an indication of adrenal cortical under-function²⁰³⁵, a view which may be valid for the terminal, pre-mortal

phase of the disease, but hardly for its clinical course. For the latter, the opposite findings, obtained in cardiac persons who had died prematurely from other causes, may be more representative. Whether the diminution of lipids in the failing human heart¹⁵⁰ is connected with alterations of cortical function has not yet been clarified.

The above-enumerated experimental and clinico-pathological observations suggest a prominent role of corticoid-induced disturbances in myocardial electrolyte balance as a causal factor in congestive heart failure, with the main emphasis on intracellular sodium accumulation, probably accompanied by a loss of intracellular potassium. This concept has been directly or indirectly propounded by several workers^{401, 402, 476, 481, 491}. It was pointed out that the cation exchanges across the cell boundary are related to metabolic activities of the cell and to the expenditure of energy rather than to merely passive transfer, resulting from differential impermeabilities⁴⁰¹. This interpretation is compatible with the fact that mineralocorticoid activity alters the intracellular electrolyte concentration and its gradient relative to extracellular fluids in a direct specific fashion which is apparently much less dependent upon the degree of renal electrolyte excretion and serum electrolyte levels than generally believed and which may be linked in a still obscure manner to cellular metabolic processes.

The exact functional significance of the corticoid-induced myocardial electrolyte imbalance for the origin and clinical course of congestive heart failure is still far from being clearly understood. However, two mutually related aspects can be considered in general terms as probably bearing on the fundamentals of this complex problem. One of them concerns the specific role of the potassium ion, attached to the organic phosphoric acid compounds, in myocardial energy production^{473, 474}, and the diminution of both potassium and phosphorus in the failing heart^{421, 430, 441}. The other aspect deals with the influence of alterations of the intracellular electrolyte concentration upon the cellular electrostatic charges and upon the electric membrane potentials, which, in turn, determine the contractile power of the muscular cells^{1000, 1002} and their dynamic response to the depolarizing agents (epinephrine and nor-epinephrine^{494, 495, 496}). No details are yet available regarding the interrelationships of these two aspects.

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On the other matter, in conjunction with the catecholamine-potentiating thyroid hormone, are prominently involved in the development of congestive heart failure.

Many of the common precipitating causes of cardiac decompensation, such as infections, pregnancy, traumatic injury, physical over-exertion, temperature changes⁴³⁵, emotional strain and various types of tachycardia, belong in the category of stress situations which are accompanied by both

asphyxial changes in the postulated venomotor centers²¹⁵⁹, and concerning a direct venopressor effect, elicited by a diminished oxygen tension in the venous blood²⁰⁶⁰, which might apply in particular to the elevations of venous pressure in anemia; but here again conclusive evidence still remains to be presented.

As could be gathered from the foregoing, there are some workers who attribute less significance to the phenomenon of *hypervolemia* as the principal factor in venous congestion than earlier investigators^{1129, 2307, 2571}. While it is true that an experimentally induced increase of the circulatory volume by itself is incapable of maintaining a raised venous pressure in the otherwise healthy organism¹⁹⁰³, elevations of the venous pressure were observed in humans with failing hearts following infusions of saline solution²⁷⁹⁵. Furthermore, a reduction of the circulatory volume of patients in congestive heart failure by means of venesection or induced diuresis, is accompanied by a prompt fall of venous pressure²¹⁶⁰. Thus, it appears evident that *hypervolemia*, though not invariably present³⁶⁷², can constitute one of the major complications contributing to the full-blown clinical picture of congestive heart failure.

Among the factors which are believed to initiate its development by interfering with salt and water excretion, both a deficiency of glomerular filtration rate, presumably due to a reduction of renal plasma flow^{2315, 2316, 2364}, and an increased tubular reabsorption of salt and water^{434, 1080} have been accused. In general, the water retention seems to exceed that of sodium²³³³ but the latter suffices nevertheless to cause a marked augmentation of total body sodium in patients with congestive failure and edema^{3402a}.

The mechanism by which a decrease of cardiac output restricts renal plasma flow as a feature of "forward" failure is still obscure. It would appear that the reduction of plasma flow through the kidneys might be a partial feature of the general arteriolar constriction which usually maintains an adequate blood pressure level in congestive failure despite the reduction of cardiac output, and which has been interpreted as a result of sympathetic stimulation, mediated by the peripheral pressoreceptors¹⁰⁶⁰. However, the persistence of renal plasma flow reduction after sympathectomy²³¹⁶ and after high spinal anesthesia^{2363, 3429} makes it improbable that renal vasoconstriction in congestive failure is caused by direct nervous interference. Instead, the theoretical possibility of a humoral action on the afferent arterioles of the kidneys has been considered²³¹⁶. There is little that would suggest an involvement of the posterior pituitary hormone, except that an antidiuretic substance was found in the urine of decompensated patients²²⁴. A passage of increased amounts of circulating adrenosympathogenic catecholamines through the renal arterioles might conceivably favor local con-

striction. The presence of antidiuretic ferritin (VDM) and of VEM in the renal venous blood in congestive heart failure^{110, 121} suggests further eventualities. For the time being, the problem remains undecided. Whether the answer to the question of the origin of diminished renal filtration rate will also solve the problem of salt retention appears doubtful, since the correlation between glomerular filtration rate and excretion of sodium chloride seems to be less intimate than originally believed¹⁰². Indeed, it has been assumed that the tubular reabsorption of salt is specifically increased in congestive failure apart from the reduction of filtration rate¹⁰⁴.

Several workers in the field of congestive heart failure^{110, 111, 122, 123} were impressed by the accumulating, though largely indirect evidence in favor of an exaggerated *adrenal cortical activity* as an important factor in the mechanism of salt and water retention, producing hypervolemia and edema. The striking analogies between the clinical picture of congestive heart failure with that of desoxycorticosterone over-dosage, the occurrence of congestive failure in cases of hyperadrenocorticism, its absence or disappearance respectively in hypoadrenocorticism and after adrenalectomy, the positive results of special tests for increased mineralocorticoid activity (urinary hormone excretion, sweat and saliva sodium assay) and certain morphological criteria—all were discussed in previous sections (p. 98, 114 ff., 494, 32). These observations leave hardly any doubt that adrenal corticoids are deeply involved in the pathogenesis of congestive heart failure by their effect on tubular reabsorption.

In the discussion of the synthesis of corticoids (p. 40), the mutual transformation of these two types of corticoids, the problem of inheritance of both mineralocorticoid and glucocorticoid functions in one single compound (F)¹²⁴, and selective steroid inactivation by the liver. Preliminary observations by the writer and his coworkers¹²⁵ suggest that it is not possible to counteract efficiently the presumable mineralocorticoid activity and its influence on sodium and water retention in congestive heart failure by the administration of supposedly antagonistic glucocorticoids (E-schatin) (Fig. 87).

The plasma sodium concentration does not clearly reflect the degree of renal sodium retention. In cases of congestive heart failure, it was found elevated¹²⁶ or normal or even slightly diminished^{100, 101, 127}. The latter was attributed both to hemodilution¹²⁸ and to intracellular deviation of sodium¹²⁹. This would be consistent with the specific effect of DCA which augments intracellular sodium^{64, 112, 129, 130} but does not significantly alter the plasma sodium level^{131, 132}.

Except in cases of the hyperadrenocortical syndrome and of DCA-over-dosage, no conclusive data are yet at hand concerning the question as to

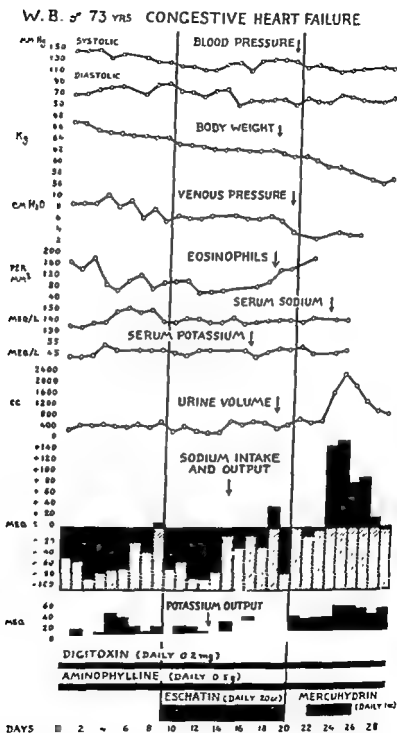


FIG. S7 Failure of adrenal cortical extract (Eschatin) to significantly affect the electrolyte output of a patient with chronic congestive heart failure during a period of constant sodium intake
(After W. Raab and N. Makous, unpublished)

whether adrenal cortical over-activity in decompensated individuals is a primary or a secondary phenomenon. In the latter eventuality, it might be attributable to the effect of forward or backward failure or both on the adrenal glands themselves, or it might be caused by general circulatory tissue hypoxia, acting on the adrenals as a stress phenomenon by mediation of the pituitary anterior lobe.

Apart from adrenal cortical interference, the water and salt-retaining effects of sexual steroids (p. 55, 190) must likewise be kept in mind as theoretically possible factors in congestive failure but data to substantiate their actual role in this condition are lacking so far.

While the thyroid hormone does not seem to exert any significant direct influence on kidney circulation and function¹⁵⁶, it can be assumed to contribute to the unfavorable status of myocardial oxygen economy of the failing heart. Even in physiological quantities (see preceding section), it acts as a potentiator of hypoxizing catecholamine action, and thus it participates probably as a subsidiary factor in the development of those cardiac metabolic disturbances which constitute the basis of congestive heart failure. The common elevation of the basal metabolic rate in congestive failure, which may reach levels as high as plus 60 per cent^{157, 158, 159, 227, 247, 270}, suggests either an increased activity of the thyroid itself or, more probably, an intensification of combined thyroid-adrenosympathetic effects on general oxidative metabolism under the additional potentiating influence of increased adrenal cortical secretion¹⁶⁰. The therapeutic effectiveness of thyroid inactivation in some cases of euthyroid congestive cardiac failure (p. 308 ff.) emphasizes the partial pathogenic significance of thyroid function.

What has been said in the preceding paragraphs regarding hormone-induced salt and water retention and resulting hypervolemia applies in principle also to the origin of cardiac edema, except in those cases in which edema formation is initiated chiefly by coexisting hypoproteinemia, as in the nephrotic state and in malnutrition, and by abnormal capillary permeability. The latter condition appears to be of only minor, if any, importance in true cardiac edema, as concluded from the low protein content of edema fluid^{161, 227}. Venous and capillary hydrostatic pressure used to be formerly considered the sole cause of cardiac edema but is no longer regarded as a primary factor, since renal retention of salt and water

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of cardiac edema in accordance with the areas of highest capillary pressure^{1060, 3243} still confirms a significant participation of the latter in the symptomatology of congestive heart failure.

Neurohormonal and Hormonal Aspects of Dyspnea and Pulmonary Edema

Although the term "*dyspnea*" in the strict sense of the word denotes the uncomfortable subjective sensation connected with an involuntary, abnormally rapid and shallow type of breathing, it is frequently also applied to the underlying respiratory pattern itself and we shall adhere to this usage of the term in order to avoid cumbersome circumscriptions.

Obviously, all varieties of cardiac dyspnea, occurring in patients with congestive heart failure, are in the last analysis ascribable to the existing derangement of cardiac dynamics, and thus everything that was said in the preceding sections regarding hormonal factors in the origin of congestive heart failure concerns indirectly also the pathogenesis of cardiac dyspnea. However, as in most regulatory disturbances of visceral function, a number of directly interfering mechanisms must also be taken into consideration.

The principal causal feature of cardiac dyspnea is left ventricular or auricular failure with resulting pulmonary congestion. The latter contributes to the development of dyspnea in several ways, which will be listed below in the approximate order of their frequency of occurrence:

(1) Engorgement of the pulmonary vessels with blood produces rigidity of the lung tissue which interferes mechanically with pulmonary expansion and retraction, congestive swelling of the alveolar walls²³⁷ hampers the gaseous exchange between alveolar cavities and capillaries,

(2) Increased pressure inside the pulmonary vessels activates the Churchill-Cope reflex⁶²³ which sends impulses to the brain, resulting in the motor phenomenon of hyperpnea¹²⁸⁴. The Hering-Breuer reflex mechanism is said to be disturbed by the incompleteness of alveolar deflation. Vagal pathways are the main route of conveyance of these reflexes^{264, 818},

(3) Incomplete oxygenation of the arterial blood, coming from the congested lungs, may combine with the low cardiac output of "forward" failure so as to reduce the oxygen supply for the respiratory centers sufficiently to elicit centrogenic hyperpnea. This factor seems to be limited to severe, advanced cases^{622, 1033, 2770},

(4) Local accumulation of unoxidized lactic acid in the respiratory centers^{1133, 2146} and more lactic acid reaching these centers from the peripheral tissues as a result of insufficient oxygen supply, are believed to act as central respiratory stimuli,

(5) A decreased ability to disperse internal heat on account of vasocon-

striction in the skin²²² has also been suspected as stimulating hyperpnea in patients with congestive heart failure²⁶.

Right ventricular failure, if developing as a secondary complication in the presence of pulmonary congestion, may alleviate the latter by pumping less blood into the engorged pulmonary vessels. Otherwise, right-sided heart failure may interfere with the mechanics of respiration through space-consuming congestive enlargement of the liver and ascites, and by eliciting reflexory stimulation of the respiratory center from the distended venae cavae and right auricle¹²⁷.

The phenomenon of *orthopnea* is ascribed to a betterment of vital capacity in the semi-recumbent or upright position because of a more efficient utilization of breathing mechanisms, because of a reduction of venous return into the congested lungs (lit., see ²⁰), and possibly because of a diminution of venous congestion in the cerebral respiratory center¹²³.

It appears evident from the foregoing discussion that there is no reason to ascribe to hormonal influences any major direct participation in the mechanisms of the ordinary types of cardiac dyspnea at rest. By contrast, it seems obvious that acute adrenosympathogenic neurohormonal discharges can be assumed to be largely responsible for the more or less severe aggravations of dyspnea during and after physical exertion, emotional excitement and other forms of stress, and for spontaneous attacks of paroxysmal dyspnea, particularly those associated with pulmonary edema.

The sequence of events leading to *dyspnea on exertion* is one of the earliest manifestations of left-sided heart failure and usually precedes *orthopnea* and *dyspnea at rest*. It is without doubt closely linked with the adrenosympathogenic discharges of epinephrine and nor-epinephrine which invariably accompany physical exertion^{467, 242} (except in radically sympathetomized individuals), apart from reflexes which are believed to originate in the skeletal muscles^{443, 127}, and to act directly on the respiratory center.

It is known that injection of epinephrine increases the respiratory volume^{172, 2012, 2224}. This effect has been ascribed to an epinephrine-induced augmentation of general metabolism⁴⁶⁷, to an increase in circulating lactate^{47, 412}, and to a direct stimulating action on the respiratory center. There -

... deviation from normal conditions rests rather with the altered hemodynamic and cardiac response to the action of presumably physiological adrenosympathogenic discharges. Circulating nor-epinephrine

and epinephrine produce a marked elevation of pulmonary arterial pressure¹⁷³. Since the pressure in the pulmonary circulation is elevated from the beginning in left-sided failure and since dyspneic reflexes are elicited by increases of pulmonary vascular tension¹²³, it appears probable that any further augmentation of pulmonary arterial pressure, as brought about by catecholamine discharges during exercise, will intensify hyperpneic responses. This may not be the only factor leading to exertional dyspnea in congestive failure, however. Reflexes from the distended right auricle in which the blood pressure rises higher than usual¹²⁷ can be assumed to participate, and an accumulation of non-oxidized lactic acid in the blood may occasionally act as an additional stimulus to the respiratory center in association with more severe exercise¹⁶⁹. Finally, the chemical effect of acutely discharged catecholamines in the heart muscle itself may bring the local hypoxia-producing oxygen wastage to a maximum and thus exhaust myocardial dynamic reserves to the point of a temporary further decrease of cardiac output and augmentation of pulmonary congestion.

Paroxysmal dyspnea shows a characteristic tendency to occur during sleep in persons who are otherwise free of marked respiratory distress but in whom a certain degree of pulmonary congestion exists between attacks³⁴⁴. Several factors are probably involved in its origin, most of which are, however, purely conjectural, such as an assumed abnormal accumulation of carbon dioxide and lactic acid in the blood due to depressed sensitivity of the respiratory center during sleep until highly stimulating concentrations are reached, influx into the vascular system of resorbed edema fluid which would increase the circulatory volume and venous return to the engorged lungs^{403, 2563}; unintentional movements in bed toward a more supine position conducive to orthopnea. Neurogenic sympatheticotonic mechanisms have been suspected as going into effect in connection with exciting dreams²¹⁴⁰. The preventive action of morphine, a vagotropic drug, seems to corroborate this concept.

There exist fluctuant transitions and apparently intimate pathogenic relations between attacks of paroxysmal dyspnea and those of *pulmonary edema* which can be described as sudden intensifications of the pulmonary congestion of left-sided heart failure¹⁰⁶⁰. More than any other form of respiratory difficulty connected with congestive heart failure, the syndrome of pulmonary edema reveals distinct indications of a *sympathogenic neurohormonal origin*. Luisada²¹⁰¹, who has contributed much to an at least fragmentary understanding of its underlying mechanism, makes a point of setting his "neurogenic" theory against the older conceptions which had placed greater emphasis on the assumption of an acutely exacerbated left

ventricular failure. However, as we shall see, it does not seem necessary to exclude this latter factor for which a number of cogent criteria have been adduced in the past. Neuro-secretory interferences may very well be held responsible simultaneously for acute aggravations of the dynamic discrepancy between right and left heart, which lead to a sudden maximal increase of pulmonary engorgement, and for a suddenly developing state of abnormal capillary permeability in the lungs, promoting the entry of plasma into the alveolar cavities. Marked elevations of the systemic blood pressure do also seem to contribute to the origin of pulmonary edema through still unexplored reflex mechanisms^{210a}.

The role of a primary hemodynamic factor, namely of blood being trapped in the lungs by the intensified pumping activity of a vigorous right ventricle, while removal by the left heart lags, is exemplified by the attacks of pulmonary edema in cases of mitral stenosis. They occur under conditions which are accompanied by a sudden increase of venous return into the right heart, such as physical exertion and childbirth^{190 211 212 213}. Apart from the stable anatomic impediment of the stenotic valve against which blood is piling up in the small circuit, there are instances of pulmonary edema due primarily to a sudden augmentation of the circulatory volume (e.g., infusions) which a failing left ventricle is unable to handle, in others, a sudden weakening of the left ventricle, caused, e.g., by a fresh myocardial infarction, accounts for acute maximal pulmonary congestion. The often observed beneficial effect of venesection or of application of tourniquets to the extremities in alleviating pulmonary edema, serves as further evidence in favor of the hemodynamic element involved¹⁰⁰.

The occurrence of pulmonary edema in connection with cerebral injuries²¹⁴, disease of the brain (lit., see²¹⁵), intra-arterial injection of fibrin^{216a}, and experimental perfusion of the brain under pressure¹⁰⁸ cannot be directly compared with the pulmonary edema occurring in patients with congestive heart failure. However, it furnishes convincing proof of the existence of neurogenic forms of pulmonary edema and encourages the search for similar, if not identical, neurogenic mechanisms in clinical cases of cardiac pulmonary edema.

Principal attention has been paid to the sympathetic system and to the sympathogenic catecholamines as overpowering the vagal counter-regulation both in experimental and clinical pulmonary edema for the following reasons:

(a) There exists some experimental evidence that permeability of the pulmonary capillaries is affected by neurovegetative stimuli, whereby the vagus exerts a tightening influence in contrast to a presumable opposite effect of the sympathetic²¹⁷.

(b) Infusion of saline solution in animals produces pulmonary edema

only if preceded by vagotomy^{409, 945} which is also capable of precipitating pulmonary edema by itself (lit., see ²¹⁰¹); pulmonary edema is intensified by atropine which eliminates vagal action and leaves the sympathetic system in control²¹⁰¹. The pulmonary edema which is induced by vagotomy can be suppressed by ergotamine²⁷⁹⁹;

(c) Pulmonary edema can be elicited by experimental stimulation of the stellate ganglia³⁹⁶ and was induced unintentionally by surgeons manipulating these ganglia^{6,6, 1673};

(d) Clinical pulmonary edema can be stopped in some cases by digital compression of the carotid sinus (vagal stimulation)²⁵¹²;

(e) Morphine which possesses specific vagotropic properties²¹¹⁴ is one of the most effective drugs for the therapeutic abolition of pulmonary edema;

(f) Attacks of pulmonary edema are usually accompanied by other signs of sympathetic stimulation, such as tachycardia, elevation of the blood pressure, superficial vasoconstriction and perspiration^{1328, 2038, 2916, 3310};

(g) One of the easiest methods to evoke pulmonary edema in experimental animals is the injection of large doses of epinephrine (lit., see ¹¹⁶³);

(h) The fatal effect of toxic, pulmonary edema-producing doses of epinephrine can be prevented by preceding bilateral cervical sympathectomy^{729, 2101} and by adrenergic blocking agents^{1241, 3290}. The latter applies also to pulmonary edema provoked by cerebral injury²¹⁶⁹. Opinions regarding a protective effectiveness of antihistaminic drugs are divided^{1241, 3290}.

(i) Pulmonary edema occurs as a common complication in cases of pheochromocytoma during hypertensive paroxysms (p 85), furthermore in uremia^{1463, 2101}, a condition in which evidence for the presence of excessive amounts of epinephrine in the blood is available (p 478 ff.), in beri-beri (p 437) which is characterized by epinephrine over-activity, and finally in many cases of "hypertensive" heart disease in which adreno-sympathogenic influences are also believed to play a leading part (p 459). The neurovegetative situation in cases of "hypertensive" heart disease includes probably an increased neurosecretion of nor-epinephrine which, although somewhat less potent than epinephrine in this particular respect, is also capable of provoking pulmonary edema²¹⁷⁰.

A review of the above-enumerated clinical and experimental observations suggests that the role of the *adrenosympathogenic neurosecretory system* in the pathogenesis of pulmonary edema in patients with impending or established chronic congestive heart failure is a dual one: (1) its acute stimulation by exertion, emotions and other less conspicuous circumstances *increases pulmonary capillary permeability* which in the presence of pulmonary congestion will result in a flooding of the alveoli with a relatively protein-rich transudate⁷⁹⁷, (2) the *degree of pulmonary engorgement may be simultaneously intensified* to the critical point of pulmonary edema

formation in those cases in which the associated elevation of the blood pressure and direct metabolic action of acutely discharged epinephrine-nor-epinephrine upon the heart cause a maximal exhaustion of myocardial functional reserve, and thus produce a transitory accentuation of left ventricular failure

Treatment

In keeping with the purpose of the present review, the subject of treatment of congestive heart failure will be discussed with primary regard to its neurohormonal and hormonal aspects. Beside a consideration of those therapeutic procedures, which constitute a deliberate direct attack on the neuroendocrine and endocrine system of patients in cardiac failure, an attempt will be made to evaluate also the neurohormonal and hormonal implications of some of the common forms of treatment for congestive heart failure, such as salt restriction, digitalis, and rest. It will not be necessary to elaborate on technical details, dosages, specific indications, etc., as these are excellently described in several recent textbooks^{425 1060 1171 1174, 1241 2102 2957 3193}

Lumbodorsal sympathectomy, although widely and successfully applied in patients with "hypertensive" heart disease in the non-decompensated or medically compensated stage (p. 470 ff), was until recently regarded by most surgeons as contra-indicated in the presence of congestive heart failure, even though P. D. White²⁴³¹ had considered its feasibility as early as 1945. South American²⁴³² and North American²⁴³³ workers, who had achieved only irregular and temporary benefit with sympathetic surgery in decompensated hypertensive individuals, did not advocate its use on a larger scale, but more favorable results were reported in 1948 by Ishberg and Pret¹⁶²¹. Five out of 16 of their decompensated cases survived more than five years after the operation. An emphatically optimistic attitude is taken by Chavez and Méndez²⁴¹² in view of the fact that out of 11 patients

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... remaining three died from uremia, cerebral hemorrhage and thrombosis, respectively. Another instance of complete recovery from severe cardiac failure of one year's duration with a-cutes and anginal pains within a week after sympathectomy, as well as two cases of congestive failure who recovered after alcohol injection of the thoracic sympathetic ganglia, have been published by Flothow¹⁰⁶⁷.

While these remarkable results were interpreted in terms of diminished

blood pressure "load" and of an alleged coronary dilatation, it seems much more probable that a diminution of the influx of adrenosympathogenic catecholamines and of their local hypoxiating metabolic action on the diseased heart muscle which renders its energy utilization dynamically inefficient (p. 11 ff.), constitutes the primary therapeutic factor. Even if the cardiac nerve supply is left intact, the elimination of large sections of catecholamine-producing tissue and of adrenal medullary secretion can be assumed to free the heart from a significant portion of its chemical catecholamine "load". In the heart of one sympathectomized patient the catecholamine concentration was found reduced to a minimum⁴⁶².

Adrenolytic drugs do not seem to have been tried in patients with congestive failure, but there is little hope that they might prove therapeutically effective since their antiadrenergic action is in general much less noticeable on the heart muscle than on the vascular system

Inactivation of the thyroid gland as a means to combat congestive heart failure was successfully applied not only in decompensated "thyrocardiacs" but also in euthyroid patients. The method of subtotal or total thyroidectomy, which was introduced in 1933 by Blumgart and his co-workers³⁹⁴, is practically abandoned today because of the availability of equally effective non-surgical procedures. Nevertheless, it may be of interest to review briefly the results in patients with congestive heart failure, obtained by the originators of this therapeutic approach and by other workers, as compiled in a survey which was published in 1939 by Blumgart and Riseman³⁹⁵. The early results in a total of 325 cases consisted of marked improvement in 32 per cent. Later check-ups in 35 patients, operated upon more than four years before³⁹⁵, revealed persistent absence of edema in seven despite physical activities which had been impossible before the operation. Many others had remained free from congestive failure and had been well for one to four years before death ensued. Patients with syphilitic heart disease and malignant hypertension responded less favorably than those with other types of congestive failure. Results, comparable with the ones obtained by thyroidectomy, were observed during administration of thiouracil^{29,27} or methylthiouracil^{450, 451, 407,5}. With a daily dosage of 400-500 mg. of the latter drug, marked and prolonged improvements occurred after four to six months of medication in four out of a group of seven cases. According to two other reports, 14 out of 23^{450, 451} and four out of seven patients responded with clinical improvement. No direct relationship with the behavior of the basal metabolic rate was noted^{450, 451}. In some of the cases, the medication had to be discontinued because of toxic side effects whereupon the cardiac signs promptly returned^{407,8}.

Treatment with radioactive iodine^{390a, 391, 1610,5} (a total of 26 to 125 milli-

curies) produced hypothyroidism and proved strikingly effective in 19 out of 45 patients who had been incapacitated by congestive failure; 10 were moderately improved. Whether or not the disadvantages, inherent in the hypercholesterolemia which results from all forms of thyroid inactivation, will in the end outweigh the therapeutic gains offered by these forms of therapy, remains to be concluded from larger series of observations.

As far as the rationale of antithyroid therapy in congestive failure of euthyroid patients is concerned, the writer is inclined to attribute its beneficial results essentially to the direct effect of induced hypothyroidism upon the metabolism of the heart muscle. It eliminates the potentiating influence which even normal amounts of the thyroid hormone exert on the hypoxia-producing oxygen wastage by which the sympathomimetic catecholamines seem to render the work of the damaged heart muscle inefficient.

Total and subtotal bilateral adrenalectomy has not yet been carried out for the treatment of congestive heart failure as the primary indication, but among the severely hypertensive patients who were subjected to this radical operation, there were several with marked congestive heart failure, all of whom were freed of their cardiac symptoms (p. 472 ff.), and the same beneficial effect was obtained by partial adrenalectomy in a case of Cushing's disease with cardiac decompensation¹²⁴. In view of the apparent involvement of adrenal cortical activity in the pathogenesis of congestive heart failure in general (p. 493, 499), it seems unlikely that the curative effect of adrenalectomy in the above-mentioned hypertensive cases should have been caused merely by lowering of the blood pressure level. Rather does it appear probable that elimination of the sodium-retaining corticoids and their replacement by maintenance doses of glucocorticoids may have improved both the electrolyte situation within the presumably sodium-loaded myocardium (p. 494) and the congestion-aggravating hypervolemia. Besides, removal of all adrenal medullary tissue may have contributed to an amelioration of myocardial oxygen economy.

The often dramatic therapeutic effectiveness of dietary sodium restriction in patients with congestive failure, implies a certain analogy with that of adrenalectomy in that it achieves by withholding extraneous sodium what adrenalectomy achieves by the reduced ability to retain ingested sodium extra- and intracellularly. The practice of restricting alimentary salt intake as a treatment of edematous patients dates back to the Karrel milk diet which was introduced in 1866¹²⁵. Systematic studies with other salt-poor regimes by Schroeder (1911)¹²⁶, Schemm (1912)¹²⁷, Kempner¹²⁸ and others^{129, 130, 131, 132, 133} revealed that in order to be fully effective, the salt-poor diet must not contain more than one to maximally two grams of sodium chloride per day, and that simultaneous fluid restriction is not an

essential feature, as formerly believed. While the opinions regarding the merits and hazards of actually forcing fluids to 5000 cc and more within 24 hours²⁹⁷³ are divided, a daily intake of two to three liters of water is now being considered appropriate^{2440, 2540}, if accompanied by rigid sodium restriction. The withholding of salt is equally useful in cases of peripheral edema and in those with mere pulmonary congestion due to left-sided failure.

In many cases it is necessary to maintain a strict salt-poor diet indefinitely but in other instances it is possible to let the patient gradually return to a more varied and palatable regime. Periodical controls of body weight and of urinary chloride excretion are necessary to evaluate the patient's progress objectively and to discover surreptitious ingestions of salt.

Extreme salt restriction is contra-indicated in persons with kidney disease whose inability to conserve the necessary minimum of sodium by tubular reabsorption may lead to hyponatremia, general weakness, azotemia, acidosis, anuria, and vascular collapse. In such cases, the corrective administration of sodium chloride may become necessary²²⁴³. According to Relman²⁷⁷⁵, the amount to be given can be estimated by means of the following formula: $A = (142 - P) \times B$ "A" stands for the required amount of sodium, expressed in milliequivalents. 142 is the average normal serum sodium concentration (milliequivalents per liter). "P" stands for the patient's actual serum sodium level (milliequivalents per liter) and "B" for his calculated total body water in liters. The latter can be assumed to be approximately 60 per cent of his ideal body weight in kilograms. If the patient is not dehydrated but edematous and hyponatremic, the required sodium should be administered in hypertonic solution (up to 5 per cent saline). Each 100 cc of a 5 per cent saline solution contains 86 milliequivalents of sodium. The infusions must be given under careful supervision and with greatest vigilance because of the danger of precipitating pulmonary edema.

Since the re-introduction of salt-poor diets, the use of *mercurial diuretics and acidification with ammonium chloride* has lost its dominant position among the therapeutic procedures intended to promote diuresis in decompensated patients. Nevertheless, these remedies still retain much of their practical importance because of the psychological difficulty to keep rigid salt-poor diets over long periods of time. The mode of action of the mercurial diuretics is generally assumed to consist of an inhibition of renal tubular reabsorption of water and sodium^{303, 805, 1377} with predominant action on the latter¹⁰⁶⁴, in apparently direct opposition to renal mineralocorticoid activity.

The combination of a salt-poor diet with mercurial diuretics and ammonium chloride beside adequate digitalization, yields particularly speedy

and gratifying results^{1167, 2140}; but here the hazard of a critical sodium depletion and dehydration^{2037, 2197} is even greater than with dietary treatment alone and careful supervision of the patient with frequent control of the serum electrolytes appears imperative.

The use of cation exchange resins permits a more liberal sodium intake, but these substances are contra-indicated in cases with renal complications and may cause the unintentional elimination of other minerals (potassium, calcium, magnesium)^{1556, 1558, 1756a, 2221}.

Certain xanthine derivatives, such as theophylline-ethylene-diamine (aminophylline) and others, are believed to improve diuresis through an increase of effective renal plasma flow¹⁴⁴² and a diminution of tubular sodium reabsorption^{1418, 1546, 2401}. Theocalcin seems to inhibit primarily the reabsorption of water²²⁰⁹. These drugs cause an increase of cardiac oxygen consumption and coronary dilatation^{258, 1011}, but are apparently devoid of the injurious hypoxiating effects of epinephrine. Venous pressure is strikingly but only transiently decreased²¹⁰⁸, an effect which proves most valuable in attacks of paroxysmal dyspnea and Cheyne-Stokes respiration.

Despite the enormous amount of work which has been devoted to the

... it is contended, it appears that their enhancing influence upon the efficiency of the failing heart is attributable to an improvement of oxygen economy^{266, 918, 1265, 2593}, thus to a mechanism which offsets the presumably exaggerated oxygen-wasting catecholamine action (p. 11 ff.) in its end effect. Experiments concerning the total oxygen consumption of digitalized heart muscle slices gave contradictory results in that increases¹⁴⁴, decreases²⁰¹⁷, or diphasic reactions²⁰⁶⁹ were observed. Gremels¹²⁰⁷ using the heart-lung preparation ...

sumption

were obtained

Contrariwise, Bing and his associates²⁰⁶, who employed the technique of right ventricular and coronary sinus catheterization in human subjects, did not detect any alterations of total cardiac oxygen consumption under the influence of strophanthus drugs either in normal or in decompensated individuals, but the cardiac output was decreased in the former and increased in the latter ... These findings ...

any major effects on the dynamics of the normal heart^{18, 1260, 1353, 2163}, but it markedly increases the contractile force and the output of the failing heart

muscle^{295, 1406, 2160, 3219, 3675}. In other words, it improves the deficient conversion of oxydative energy into mechanical work.

It seems tempting to interpret the action of digitalis on myocardial metabolism as counterbalancing that of the sympathomimetic catecholamines by activating vagal mechanisms¹²⁶⁷. This is also suggested by the slowing of the heart rate and prolongation of atrioventricular conduction time under the influence of digitalis. However, the failure of digitalis glycosides to improve the cardiac anomalies of thyrotoxicosis and beri-beri in which adrenergic over-activity appears to be most prominently involved makes a specific antagonism of digitalis against the latter doubtful. It has been shown¹⁵⁷⁶ that digitalis glycosides favor the polymerization of actin and thus contribute to the formation and energy utilizing function of actomyosin²⁴⁷⁶. An inhibition of cholinesterase activity has been suspected^{1513, 354} but could not be confirmed^{1952a}.

The old notion that the therapeutic effect of digitalis is produced predominantly by its heart-slowing action and that it is, therefore, largely limited to cases with auricular fibrillation and tachycardia^{2019, 2174} was not corroborated by further clinical experience, in that marked benefit from digitalis medication is also obtained by patients with sinus rhythm in whom the bradycardia-producing effect is of only minor, if any, significance^{131, 315, 1117, 2160, 3679}.

Digitalis-induced augmentation of cardiac output and reduction of venous and right ventricular pressure do not always coincide. In some types of congestive failure and with certain digitalis preparations (e.g., digoxin), a diminution of right ventricular and of venous pressure was observed before or in the absence of an increase of cardiac output²¹⁶⁰. It was accompanied by relief of the symptoms of pulmonary engorgement. Conversely, ouabaine was found to raise the cardiac output without a concomitant diminution of venous pressure^{15, 296}. Hence, the hemodynamic effects of the digitalis glycosides seem to be partially modified by reactions of the venopressor mechanisms, the exact nature of which is still unknown.

Increased renal excretion of sodium and water³²⁴, which results from improved cardiac effectiveness and augmented renal plasma flow, tends to reduce the circulatory volume³⁰⁵⁶ and thus contributes to a further normalization of venous pressure. No special studies have yet been devoted to the presumable indirect effect of digitalis medication on adrenal cortical function but it appears likely that whatever secondary alterations of cortical activity may have been elicited by the state of congestive failure, would be brought to disappearance by successful digitalis medication.

Whether the reduction in size of enlarged, decompensated hearts which is sometimes achieved by digitalization^{1592, 3277, 3241} is caused primarily by the diminution of hypervolemia or by a direct action on the heart muscle¹⁹⁴

has not been decided. In animal experiments it has been found that strophanthin inhibits the cardiac hypertrophy-producing effect of de-oxy-corticosterone.²¹⁹ Recent observations by N. E. Clarke and R. E. Moher (Circulation, 5: 907, 1952) did not only confirm the previously demonstrated increase of sodium²²⁰ and diminution of potassium^{221, 222} in the heart muscle of patients with congestive failure but they indicated also a normalization of this aberration of myocardial electrolyte balance under the influence of digitalis. Thus, it appears that digitalis exerts an effect on the heart muscle which results in an electrolyte situation diametrically opposite to that produced by DCA, without affecting the myocardial water content.

Morphine, possibly by virtue of its vagotropic action beside its central depressant effects, is the most potent remedy for episodes of paroxysmal dyspnea and pulmonary edema in which acute adreno-sympathogenic mechanisms seem to play a prominent part, as discussed on p. 504 ff.

Physical rest and mental relaxation have always been the basic prerequisites for the success of any therapeutic effort, directed against the hemodynamic and metabolic disturbances underlying the various types of congestive heart failure. In milder cases these elementary factors may indeed suffice to free the patient entirely of his symptoms. In the interpretation of their efficacy, emphasis is often placed on a reduction of the so-called circulatory "demands" of the body which the failing heart cannot adequately "fulfill." For scientific purposes, however, one has to consider the problem objectively in terms of an automatic sequence of cause and effect rather than from the autistic point of view of fictional "demands" and "fulfillments." Thus, discounting any alleged exchange of wishes and favors between body tissues and heart, we can consider the effects of rest largely as the result of a diminution of the adreno-sympathetic neurohormonal stimuli which tend to aggravate myocardial hypoxia and inefficiency. Rest and relaxation may be regarded as the equivalents of a partial functional sympathectomy. They permit the heart to recuperate from the biochemical strains and stresses of everyday life.

Summary

Neurohormonal and hormonal factors, whose involvement in the pathogenesis of congestive failure is suggested by the following facts:

1. ... favor the development of pulmonary edema

A contributing role of myocardial oxygen-wasting, efficiency-decreasing adrenosympathogenic catecholamines in the origin of cardiac failure can be concluded from (a) a demonstrably inadequate conversion of oxidative energy into mechanical work; (b) metabolic abnormalities in the myocardium of failing hearts, analogous to those, experimentally produced by epinephrine; (c) the presence of abnormally high concentrations of catecholamines in hearts of patients who had died in congestive failure; (d) the reported curative effects of sympathectomy which is followed by a reduction of the catecholamine concentration in the myocardium.

There are no indications of an over-function of the thyroid gland in the average case of congestive failure but even physiological amounts of the thyroid hormone suffice to maintain a state of potentiation of cardiologic catecholamine activity. Accordingly, thyroid inactivation (surgery, thiourea derivatives, radio-iodine) proves therapeutically highly effective in some cases, probably by secondarily diminishing the above-mentioned chemical catecholamine effects on the heart muscle.

While a primary adrenal cortical over-activity appears obvious in cardially decompensated patients with Cushing's syndrome and probable in those with toxemia of pregnancy and in certain cases of essential hypertension, a secondary (hypoxia-stress-induced?) cortical stimulation is believed to aggravate the clinical status of cardiac patients by (a) sodium and water retention (hypervolemia, edema); (b) alteration of myocardial electrolyte balance (intracellular Na^+ deposition, K^+ loss). Mineralocorticoid over-activity in congestive heart failure is suggested by hormone and sodium excretion tests, by morphological findings in the adrenals and by dramatic curative effects of subtotal or total adrenalectomy. The therapeutic results of dietary salt restriction and of sodium-eliminating mercurial diuretics represent in a sense functional equivalents of the sodium depletion, achieved by adrenalectomy.

Acute discharges of adrenosympathogenic catecholamines seem to contribute to the occurrence of exertional dyspnea and pulmonary edema by temporarily aggravating left ventricular inefficiency and by increasing capillary permeability. Vagal stimulation (carotid sinus pressure, morphine) is capable of counteracting paroxysmal dyspnea and pulmonary edema to some extent.

Digitalis, by activating vagal mechanisms and by improving myocardial oxygen economy, acts in the opposite direction to the oxygen-wasting sympathetic catecholamines and restores efficient oxidative energy conversion into mechanical work.

Physical and mental rest restrict adrenosympathetic neurosecretory discharges and their unfavorable interference in cardiac metabolism and hemodynamics.

SYNOPSIS OF

Neurohormonal and Hormonal Pathogenic Factors in Cardiovascular Syndromes

Some of the following interpretations, although supported by some experimental and clinical evidence, are essentially speculative and intended merely to serve as working hypotheses, especially where indicated by question marks.

ARTERIOSCLEROSIS AND RELATED VASCULAR LESIONS

Catecholamines

Discharged by vascular sympathetic nerve endings and by the adrenal medulla, (a) damage muscle cells of media of smaller arteries (through chemically induced local hypoxia?); (b) intensify lipid deposition in intima, (c) may damage renal vessels while passing through the glomeruli (?).

Sympathectomy

Retards progression of peripheral vascular disease.

Thyroid hormone

Prevents lipid deposition in intima.

Thyroid inactivation (induced myxedema) enhances intima lipoidosis

Corticoids

Mineralocorticoids damage small vessels, probably by altering electrolyte distribution.

Adrenocorticotrophic hormone and growth hormone

Enhance injurious effects of mineralocorticoids on small vessels (see above) (?).

Gonadal steroids

Prevent lipid deposition in intima (?).

Parathyroid hormone

Favors calcifying necrosis of media (?)

ARTERIAL HYPERTENSION (NEUROGENIC, HORMONAL)*Catecholamines*

(a) Nor-epinephrine, discharged from sympathetic nerve endings into arteriolar walls under central nervous stimulation (psychic tension; arteriolar sclerotic ischemia of vasomotor centers; cerebral trauma or inflammation) elevates blood pressure; (b) Diminished vagal counteraction due to reduced distensibility of carotid sinus causes preponderance of pressor action of nor-epinephrine in arterial walls; (c) By constricting renal vessels, catecholamines may contribute to formation and retention of hypothetical renal pressor substances (?).

Sympathectomy, ganglionic blocking agents, and sympatholytic drugs lower blood pressure by eliminating or inactivating catecholamine-discharging adrenosympathetic tissue or by blocking catecholamine action, respectively

Corticoids

Mineralocorticoids (DCA) enhance the pressor effects of catecholamines, probably by depositing sodium inside vascular cells and by thus increasing their electric membrane potential, which depends on the intra-extracellular electrolyte concentration gradient and which determines contractile responsiveness. They may also increase the circulatory volume. Even if not augmented, they maintain the pressor effectiveness of other agents.

Adrenalectomy: Lowers blood pressure (a) by eliminating mineralocorticoids and their indirectly pressure-maintaining effects; (b) by stopping adrenal medullary secretion

Salt withdrawal deprives the mineralocorticoids of the material by means of which they seem to augment vascular pressor responsiveness

Adrenocorticotrophic hormone

Contributes to pressure elevation via adrenal corticoids (?)

Enkephalin

May elevate pressure as a product of cerebral neurosecretion (?).

"ESSENTIAL" AND POSTURAL HYPOTENSION*Catecholamines*

Sympathetic neurosecretory discharges of nor-epinephrine or vascular contractile reactivity to pressor catecholamines, or both may be decreased (?). Locally dilator discharges of epinephrine into arteriolar walls of skeletal musculature may be increased (?).

Corticoids

Low production of mineralocorticoids by adrenal cortex may contribute to symptoms by decreasing vascular contractile responsiveness (?)

DCA elevates blood pressure.

Gonadal steroids

Some relationship suggested by occurrence during puberty, pregnancy, in cases of sexual under-function.

CAROTID SINUS SYNDROME*Catecholamines*

Counter-regulatory adreno-sympathetic discharges against acute reflexory vagal over-stimulations insufficient

SYNCOPE*Catecholamines*

Increased local dilator effects of neurogenic epinephrine (?) on vessels of musculature and other areas under hypothalamic influence (?).

Gonadal steroids

May influence cerebral and reflex mechanisms involved (occurrence during puberty, menstruation, pregnancy, menopause).

SHOCK (PRIMARY "NEUROGENIC" PHASE)*Catecholamines*

Epinephrine discharges from adrenal medulla and/or nerve terminals (?) (a) lower blood pressure by dilating peripheral vessels (especially in musculature) (?), without simultaneous increase of cardiac output because of reduced circulatory volume (venous pooling ?); (b) stimulate adrenal cortical secretion via pituitary

Epinephrine administration contra-indicated, nor-epinephrine (constrictor) useful

SHOCK (SECONDARY "COMPENSATORY" PHASE)*Catecholamines*

General vasoconstrictor nor-epinephrine preponderance (?), possibly initiated by pressure-receptor reflexes and by sensitization of splanchnic vessels to constrictor catecholamine action by VEM from ischemic kidney (?)

Catecholamine administration probably contra-indicated.

Corticoids

May possibly contribute to maintenance of high arteriolar tone through potentiation of nor-epinephrine action (?).

SHOCK (IRREVERSIBLE "DECOMPENSATORY" PHASE)*Catecholamines*

Neurogenic nor-epinephrine secretion diminished due to ischemic paralysis of vasomotor centers (?); splanchnic vasoconstrictor catecholamine action abolished by VDM from ischemic liver (?).

Corticoids

Exhaustion of adrenal cortex may contribute to non-responsiveness of vessels to pressor catecholamine action (?) and may cause myocardial weakness (?).

Corticoid administration of questionable therapeutic value.

NEUROCIRCULATORY ASTHENIA*Catecholamines*

Preponderance of labile catecholamine action on cardiovascular system; probably caused mainly by insufficient vagal counter-regulatory reactions to centrogenic sympathetic stimulation.

Gonadal steroids

Prevalence in females suggests some contributory interference of female steroids in cerebral regulation of neurosecretory activities

Thyroid hormone

Apparently not primarily involved despite clinical similarity with thyrotoxicosis with which the syndrome shares the features of sympathetic preponderance.

PERIPHERAL VASCULAR DISTURBANCES*Catecholamines*

Obscure derangements of regional neurosecretory discharges or of vascular cellular responses to local neurosecretory influences

Sympathectomy and sympatholytic drugs sometimes therapeutically effective

Gonadal steroids

Prevalence in females suggests some contributory interference of female steroids in peripheral vascular reactivity.

PERIARTERITIS NODOSA*Corticoids*

Excessive action of mineralocorticoids under anterior pituitary influence (?) as a feature of the "adaptation syndrome", possibly in

conjunction with pre-existing locally injurious "stressor" substances
(?)

Limited therapeutic action of glucocorticoids.

Adrenocorticotrophic hormone

Limited therapeutic effect.

ANGINA PECTORIS

Catecholamines

Acute influx of chemically hypoxiating catecholamines from efferent sympathetic cardiac nerves and/or adrenal medulla into heart muscle causes painful degree of myocardial hypoxia if (a) coronary arteries are sclerotic and unable to dilate adequately, (b) if quantity of catecholamines is excessive.

Catecholamine discharges during exercise are usually exaggerated in angina cases.

Sympathectomy. Therapeutically effective (a) by reducing influx of neurogenic catecholamines into myocardium and thus preventing chemical hypoxia, (b) by severing afferent pain-conveying fibers.

X-ray irradiation of adrenal glands: therapeutically effective by reducing adrenal medullary catecholamine discharges. May be combined with irradiation of cervicothoracic sympathetic.

Thyroid hormone

Potentiates catecholamine-induced hypoxia of the heart muscle.

Thyroid inactivation (surgery, thiourea compounds, radio-iodine): therapeutically effective by reducing hypoxiating effectiveness of catecholamines.

Gonadal steroids

Prevalence in males suggests some contributory interference of male steroids (or of their deficiency?) in myocardial metabolism.

Testosterone. Therapeutically effective by influencing myocardial metabolism (?).

ANOXIC MYOCARDIAL NECROSIS

Catecholamines

(a) They may contribute to the development of coronary sclerosis (see above under "arteriosclerosis"); (b) They may precipitate intramural hemorrhages by sudden dilatatory stretching of brittle coronary arterial tissue (?) and thus precipitate thrombus formation in sclerotic coronary arteries; (c) If discharged locally in excess into the heart muscle by sympathetic nerve endings, they may cause

local chemical anoxic necrosis even in the absence of coronary vascular lesions; (d) In case of fresh myocardial infarction, peripheral vasodilator epinephrine discharges may contribute to the primary shock syndrome (?); (e) Further catecholamine action upon the heart after establishment of myocardial necrosis is probably partly offset by vagal counter-regulation (Bezold-Jarisch reflex).

SUDDEN CARDIAC DEATH WITHOUT MORPHOLOGICAL SUBSTRATE

Catecholamines

Excessive accumulation in the heart muscle of over-dosed injected or excessively secreted catecholamines can cause sudden death, probably from ventricular fibrillation.

BERI-BERI HEART DISEASE

Catecholamines

Abnormally increased intramyocardial accumulation and cardiovascular action of catecholamines (especially epinephrine) cause increased cardiac output, decreased peripheral resistance, myocardial degeneration, ultimately leading to congestive heart failure

Epinephrine sensitivity ■ increased.

Corticoids

Possibly increased (cortical hypertrophy) (?)

IDIOPATHIC CARDIAC HYPERTROPHY

Possibly obscure interaction of pituitary growth hormone (?), thyroid hormone (?), corticoids (?) and catecholamines (?) on heart muscle

ATHLETE'S HEART

Catecholamines

Apparently discharged in physiological quantities but overwhelmingly counter-balanced by increased, oxygen-sparing vagal action, regarding myocardial oxygen economy and work efficiency

HYPERTENSIVE HEART DISEASE

Catecholamines

Probably augmented neurogenic discharges into myocardium in neurogenic forms of hypertension cause chronic hypoxic cardiac manifestations, hypertrophy, and ultimate myocardial damage. Sympathectomy can normalize cardiac status even if hypertension continues undiminished.

Corticoids

Mineralocorticoid over-activity may aggravate myocardial damage by altering intracellular electrolyte balance.

Adrenalectomy is capable of abolishing all cardiac abnormalities.

Adrenocorticotrophic hormone

Probably enhances corticoid effects on heart muscle (adaptation syndrome) (?)

Growth hormone

May contribute to cardiac hypertrophy and damage in conjunction with corticoids, thyroid hormone and catecholamines.

UREMIC HEART LESION*Catecholamines*

Excessive amounts circulate in the blood, probably due to renal retention, and accumulate in the heart muscle, thus contributing to myocardial damage and ultimate failure

CONGESTIVE HEART FAILURE*Catecholamines*

If present in the myocardium in excess or if not matched by sufficient vagal metabolic counteraction, the hypoxiating catecholamines impair adequate conversion of oxidative energy into mechanical work.

Acute catecholamine discharges into blood and/or heart muscle cause paroxysmal dyspnea and pulmonary edema by (a) aggravating left ventricular insufficiency and pulmonary congestion, (b) increasing pulmonary capillary permeability(?).

Sympathectomy is capable of restoring normal cardiac function.

Thyroid hormone

Aggravates the injurious action of the catecholamines by potentiation.

in the heart muscle.

Corticoids

Adrenocortical over-activity may serve as initiating factor of congestive failure or as a stress-induced secondary complication.

ret

ti

accumulation and potassium loss).

Adrenalectomy is capable of restoring normal cardiac function.

TABLE III

Presumable Pathogenic Role of Cardioxic Hypoxia-Producing Adreno-sympathogenic Catecholamines in Some Forms of Heart Disease

TYPE OF CARDIAC PATHOLOGY	CATECHOLAMINES IN BLOOD	SPECIAL ADRENO-SYMPATHOGENIC CLINICAL FEATURES	EXCESSIVE AMOUNTS OF CATECHOLAMINES IN HEART MUSCLE	MUSCULAR STRUCTURAL CHANGES, PROBABLY ATTRIBUTABLE TO HYPOXIATING CATECHOLAMINE ACTION	CATECHOLAMINE-INDUCED (?) "HYPOXIC" ELECTROCARDIOGRAPHIC CHANGES	PROBABLE CAUSE OF EXAGGERATED CATECHOLAMINE ACTION UPON THE HEART
I Angina pectoris on effort	Exaggerated acute discharges on effort	In some cases increased cardiac output and elevation of blood pressure Recovery after sympathectomy	?	Often present (even in absence of significant coronary atherosclerosis)	Usually present during attacks, on exertion, etc.	Increased irritability of adreno-sympathetic neurosecretory mechanism, myocardial hypoxia aggravated by coronary stenosis
II Sudden death without morphological substrata	?	Anginal pain, pulmonary edema preceding death	Present in 2 cases examined (and in all animals killed with epinephrine)	Occasionally present	?	Excessive acute adreno-sympathetic discharges, as precipitated by emotions, strenuous exercise, etc.
III "Hypertensive" heart disease (with or without hypertension)	Exaggerated acute discharges but normal resting levels	Occasionally tachycardia, pulmonary edema, blood pressure usually high Recovery after sympathectomy	Often present	Often present (even in absence of significant coronary atherosclerosis)	Often present ("strain pattern")	Centrogenic stimulation of adreno-sympathetic neurosecretion, potentiation of catecholamine action by corticoids (via electrolytes?)
IV Uremic heart	Regularly and constantly abnormally increased	Pulmonary edema, tachycardia, positive benzodioxane test	Usually present	Usually present	Usually present	Accumulation of catecholamines in blood and myocardium, probably due to renal retention

TABLE 21—continued

TYPE OF CARDIAC PATHOLOGY	CATECHOLAMINES IN BLOOD	SPECIAL ADRENAL ANPATHOGENIC CLINICAL FEATURES	EXCESSIVE AMOUNTS OF CATECHOLAMINES IN HEART MUSCLE	MYOCARDIAL STRUCTURAL CHANGES, PROBABLY ATTRIBUTABLE TO HYPOVASCULAR CATECHOLAMINE ACTION	CATECHOLAMINE-INDUCED (?) * HYPOXIC ECG/ECG CHANGES	PROBABLE CAUSE OF EXAGGERATED CATECHOLAMINE ACTION UPON THE HEART
V Peripheral heart	Increased (animals)	Increased cardiac output, high epinephrine sensitivity, high RMR	Usually present (animals)	Usually present	Usually present	Increased adrenomedullary catecholamine secretion (?), adrenal hyperplasia
VI The mitotic heart disease	Normal	Tachycardia, increased cardiac output, high RMR, high epinephrine sensitivity	Not present (animals)	Frequently present	Occasionally present	Abnormal sensitization of heart to catecholamine action through paracrine thyroid hormone

GENERAL SUMMARY

Regardless of the problematic character of many of the factual details and interpretations presented in this book, there emerge a few basic principles which can be assumed to constitute the essence of neuroendocrine and endocrine participation in the origin of cardiovascular pathology of various types, as far as perceivable at this time:

(1) *The adreno-sympathogenic catecholamines nor-epinephrine and epinephrine which reach all cardiovascular muscle cells from their supplying sympathetic nerve endings through neurosecretion and from the adrenal medulla via the blood stream exert a specific oxygen-wasting effect on these cells so that they convert only a disproportionately small fraction of the energy consumed into mechanical work. Thus, the catecholamines are capable of producing painful and structurally injurious hypoxia of the heart muscle and degenerative lesions of the arterial walls.*

Acute catecholamine discharges, by virtue of their instantaneous pressor and hypoxiating effectiveness, are instrumental in eliciting pheochromocytomatous hypertensive paroxysms, attacks of angina pectoris, acute anoxic myocardial necroses, acute heart failure and pulmonary edema. Chronic discharges are apparently involved in sustained pheochromocytomatous hypertension, "neurogenic" hypertension, "hypertensive" heart disease, beri-beri heart disease, and arteriosclerosis. Retention of otherwise excreted catecholamines seems to contribute to the cardiovascular complications of renal excretory failure.

(2) *The thyroid hormone intensifies the metabolic action of the catecholamines (especially of epinephrine) upon the heart muscle and thus maintains or aggravates their potentially harmful hypoxiating effectiveness. Lack of thyroid function protects the heart from catecholamine-induced metabolic hypoxia but favors the development of atherosclerosis.*

(3) *The slow acting adrenal mineralocorticoids interfere in cardiovascular electrolyte balance by increasing intracellular sodium and decreasing intracellular potassium. They potentiate the pressor effectiveness of the adreno-sympathogenic catecholamines. This principle forms probably the basis of arterial hypertension in states of adrenal cortical overfunction, as in Cushing's syndrome and "hormonal" hypertension. Adrenal corticoids are believed to contribute also to structural cardiovascular lesions, to the hypervolemia in congestive heart failure and to the manifestations of toxemia of pregnancy. Lack of mineralocorticoids depletes cardiovascular cellular sodium and thus diminishes cardiovascular muscular contractile power.*

In a condensed form, the three cardinal phenomena of potentially patho-

genic significance which concern the adreno-sympathogenic catecholamines may be kept in mind as follows:

- I . Neurosecretion of catecholamines into cardiovascular tissue.
- II . Tissue-hypoxia-producing action of catecholamines
- III . Potentiation of catecholamine action by thyroid hormone and mineralocorticoids

The role of the hormones of the pituitary, the gonads, the parathyroids and the pancreas in cardiovascular pathology is probably a less direct one and still poorly understood. The growth hormone seems to contribute to the process of cardiac hypertrophy in conjunction with the catecholamines, the thyroid hormone and the mineralocorticoids.

Some time-honored but out-dated mechanistic views which interpret cardiovascular functional and structural changes solely in terms of coronary flow and of hemodynamic factors are no longer tenable. They must be revised in the light of present-day knowledge of ubiquitous neuroendocrine and endocrine biochemical influences upon cardiovascular tissue metabolism and of their interplay. Teleological auxiliary hypotheses are becoming increasingly superfluous and should be discarded.

Remarkable progress has been made in recent years in the treatment of arterial hypertension, angina pectoris and congestive heart failure by measures, deliberately or inadvertently directed against neurohormonal and hormonal overfunction, such as sympathectomy, antiadrenergic medication and radiotherapy, surgical and non-surgical thyroid inactivation, adrenalectomy and restriction of dietary sodium, the main substrate of adrenocortical pathogenic activity. Even greater therapeutic achievements and the development of practical preventive methods can be expected of the coming era which will have to concentrate on a deeper understanding of the fundamentally biochemical nature of the commonly occurring hormonal and neurogenic cardiovascular disorders.

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